SYNTHESIS OF NITROGENOUS COMPOUNDS

SUMMARY

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

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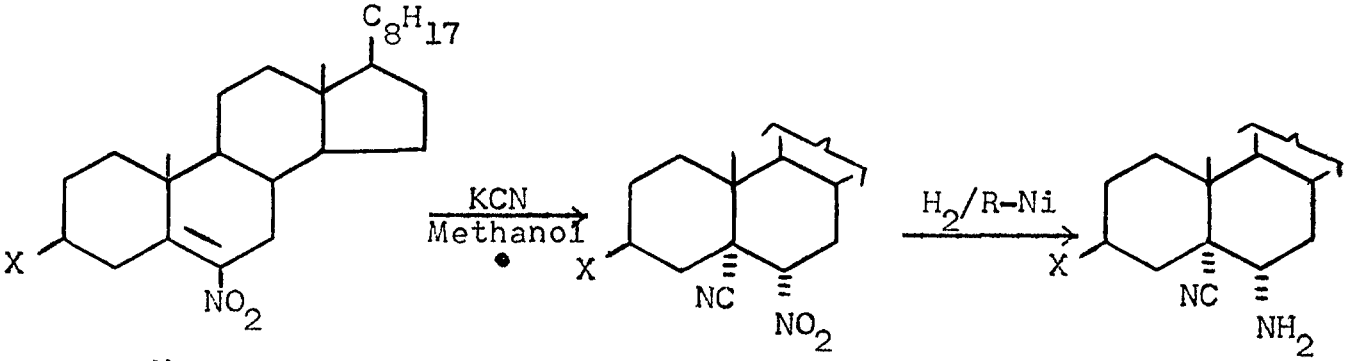
ALIGARH (INDIA)

June, 1986

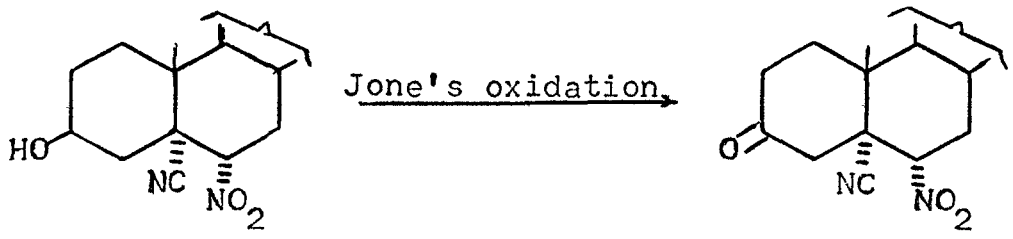
PART-1

Synthesis of steroidal cyanoamines

This section deals with the preparation of steroidal cyanoamines. Nitroolefins were treated with KCN in methanol to obtain nitrocyanides (V-VIII) and were subjected to hydrogenation in the presence of Raney-nickel as catalyst. 3β-Hydroxy-5-cyano-6α-nitro-5α-cholestane (V) on reduction with H_2/Ni gave 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (IX) and 5-cyano-6α-nitro-5α-cholestane (VII) on similar reduction provided 5-cyano-6α-amino-5α-cholestane (X). Acetoxy analogue (VI) gave product (IX) and 3β-chloroanalogue (VII) provides amine (X). Compound (XI) was obtained by the treatment of nitrocyanide (V) with Jone's reagent.

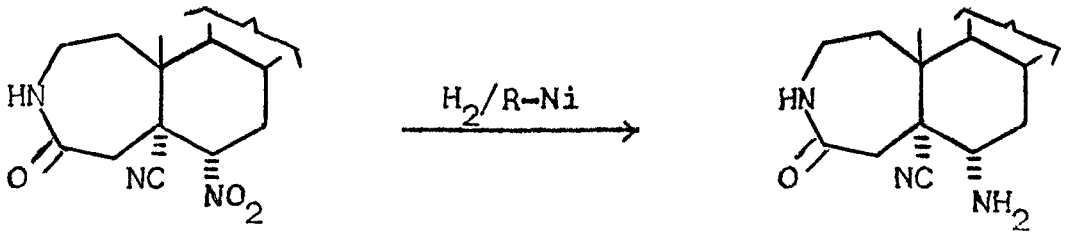


	X		X		X
(I)	-OH	(V)	-OH	(IX)	-OH
(II)	-OAc	(VI)	-OAc	(X)	-H
(III)	-H	(VII)	-H		
(IV)	-Cl	(VIII)	-Cl		

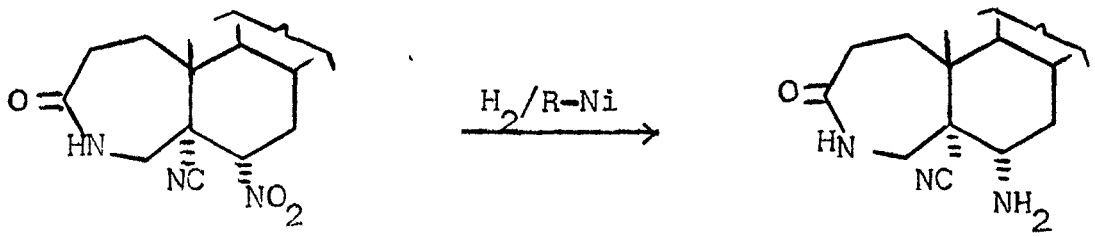


(V) (XI)

The nitrolactam nitriles (XII) and (XIII) obtained by the reaction of 5-cyano-6α-nitro-5α-cholestan-3-one (XI) with an excess of hydrazoic acid, when reduced with H_2/Ni provided the respective amines (XIV) and (XV) in the excellent yields. The lactam and nitrile function did not get affected during the hydrogenation.



(XII) (XIV)

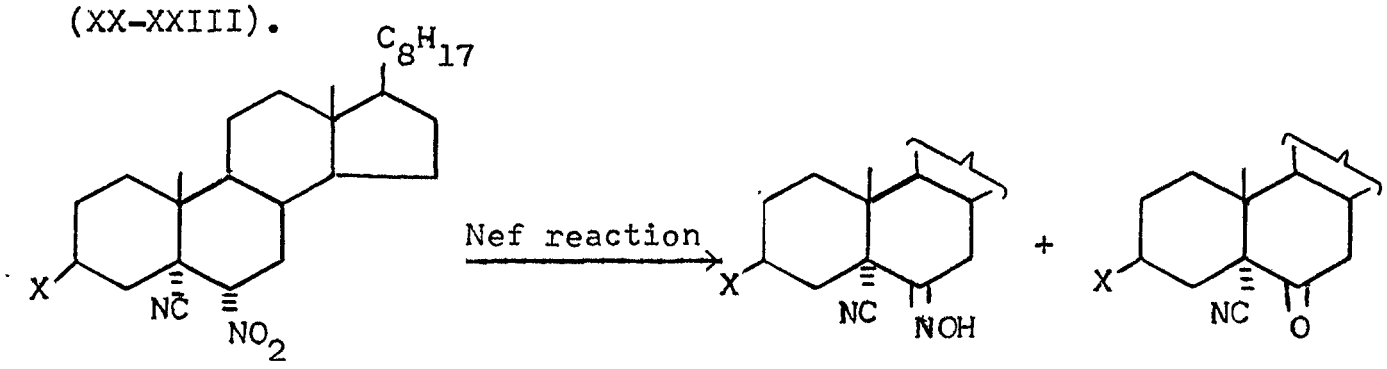


(XIII) (XV)

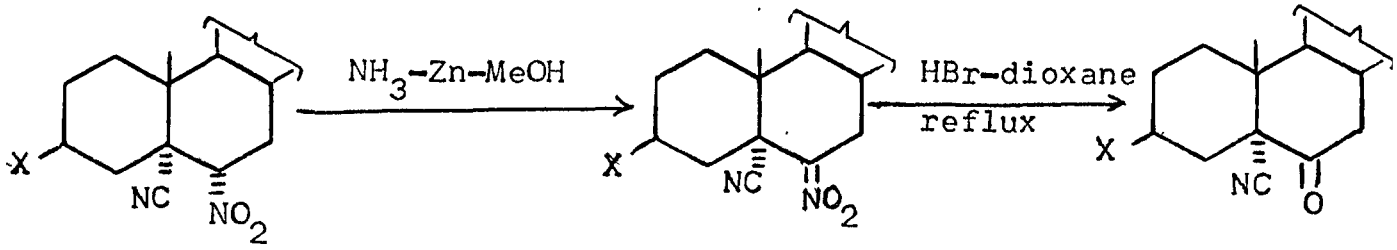
PART-2

Synthesis of steroidal α-cyanoketones

Nef reaction of 5-cyano-6α-nitro-5α-cholestane (V-VIII) has been undertaken in order to synthesise 5 -cyano-5α-cholestan-6-ones (XX-XIII). This reaction provided a mixture of respective cyanoketone and cyanooxime. Acetoxy analogues(XXI and XVII) were not obtained due to the alkaline conditions of the reaction. Nitrocyanides (V-VIII) on treatment with $Zn-NH_3$-MeOH reagent, were selectively transformed to the above cyanooximes (XVI-XIX) respectively in good yields. The oximes (XVI-XIX) were then hydrolysed with HBr in dioxane to their respective cyanoketones (XX-XXIII).

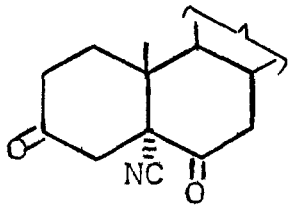


	X		X		X
(V)	-OH	(XVI)	-OH	(XX)	-OH
(VII)	-H	(XVIII)	-H	(XXII)	-H
(VIII)	-Cl	(XIX)	-Cl	(XXIII)	-Cl



	X		X		X
(V)	-OH	(XVI)	-OH	(XX)	-OH
(VI)	-OAc	(XVII)	-OAc	(XXI)	-OAc
(VII)	-H	(XVIII)	-H	(XXII)	-H
(VIII)	-Cl	(XIX)	-Cl	(XXIII)	-Cl

The cyanoketone (XX) and cyanooxime (XVI) when treated with Jone's reagent, afforded 5-cyano-5α-cholestane-3,6-dione (XXIV) and 5-cyano-6-oximino-5α-cholestan-3-one (XXV).



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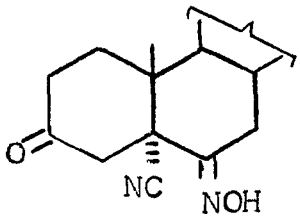
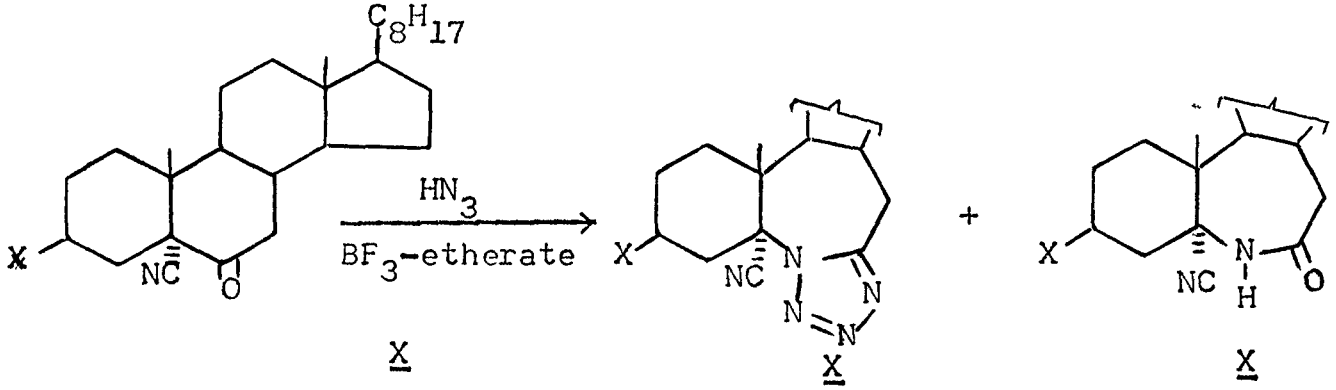


(XXV)

PART-3

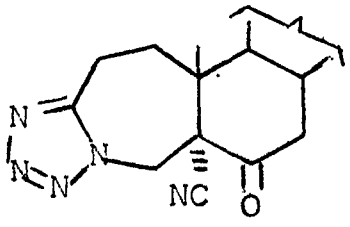
Synthesis of cyano-azasteroids

It describes the preparation of azasteroids (tetrazoles and lactams) from hitherto unreported cyanoketones (XX-XIV). The 3β-substituted 5-cyano-5α-cholestan-6-ones (XX-XXIII) on reaction with hydrazoic acid and borontrifluoride-etherate, provided the respective 6-aza tetrazoles (XXVI-XXIX) and 6-aza lactams (XXX-XXXII) in case of 3β-acetoxy-5-cyano-5α-cholestan-6-one (XXI), only tetrazole (XXVII) was obtained.

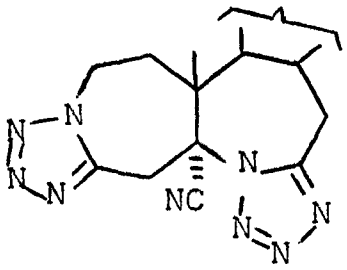


	X		X		X
(XX)	-OH	(XXVI)	-OH	(XXX)	-OH
(XXI)	-OAc	(XXVII)	-OAc		
(XXII)	-H	(XXVIII)	-H	(XXXI)	-H
(XXIII)	-Cl	(XXIX)	-Cl	(XXXII)	-Cl

Cyanodiketone (XXIV) when treated with hydrazoic acid and borontrifluoride etherate under the Schmidt reaction condition afforded 4-aza-A-homo-5-cyano-6-oxo-5α-cholestano[4,3-d] tetrazole (XXXIII), 3,6-diaza-A,B-bishomo-5-cyano-5α-cholestano [3,4-d][6,7-d]bistetrazole (XXXIV) and 3,6-diaza-A,B-bishomo-7-oxo-5-cyano-5α-cholestano[3,4-d]tetrazole (XXXV).



(XXXIII)



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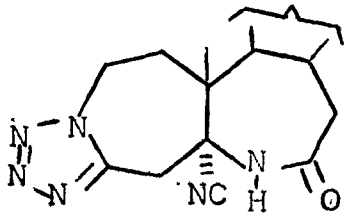
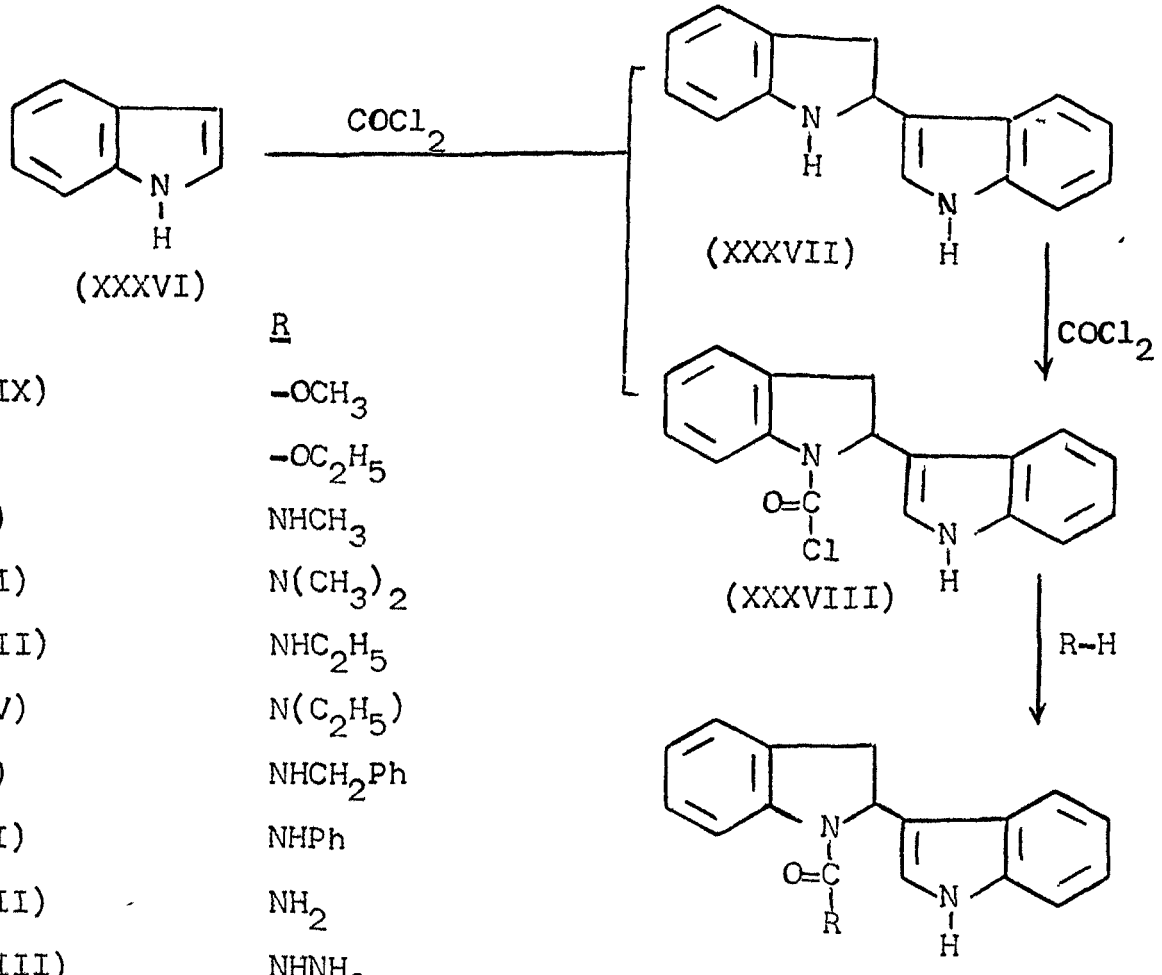


(XXXV)

PART-4

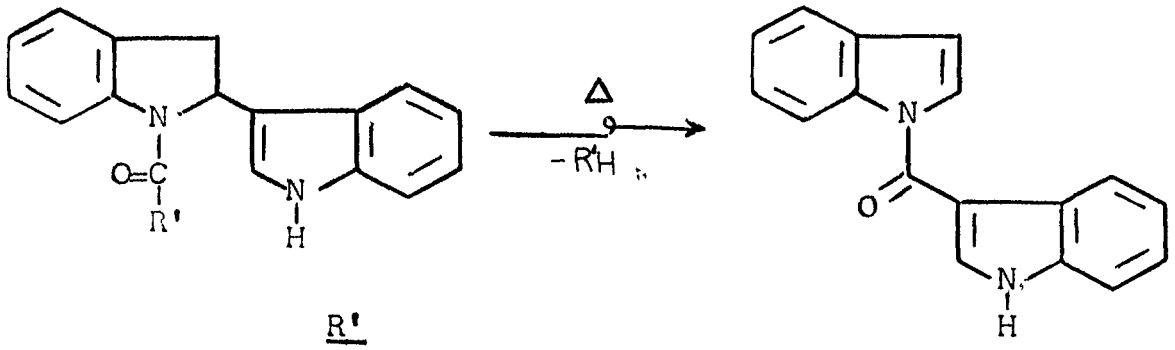
Synthesis of indole dimers

This part describes the synthesis of 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (XXXVIII) by the reaction of indole (XXXVI) with phosgene. The derivatives (XXXIX-XLIX) have been obtained by the reaction of the former with respective reagents. The indole dimer (XXXVII) when treated with phosgene also produced the carbonyl chloride (XXXVIII).



	R
(XXXIX)	$-OCH_3$
(XL)	$-OC_2H_5$
(XLI)	$NHCH_3$
(XLII)	$N(CH_3)_2$
(XLIII)	NHC_2H_5
(XLIV)	$N(C_2H_5)$
(XLV)	$NHCH_2Ph$
(XLVI)	NHPh
(XLVII)	NH_2
(XLVIII)	$NHNH_2$
(XLIX)	CN

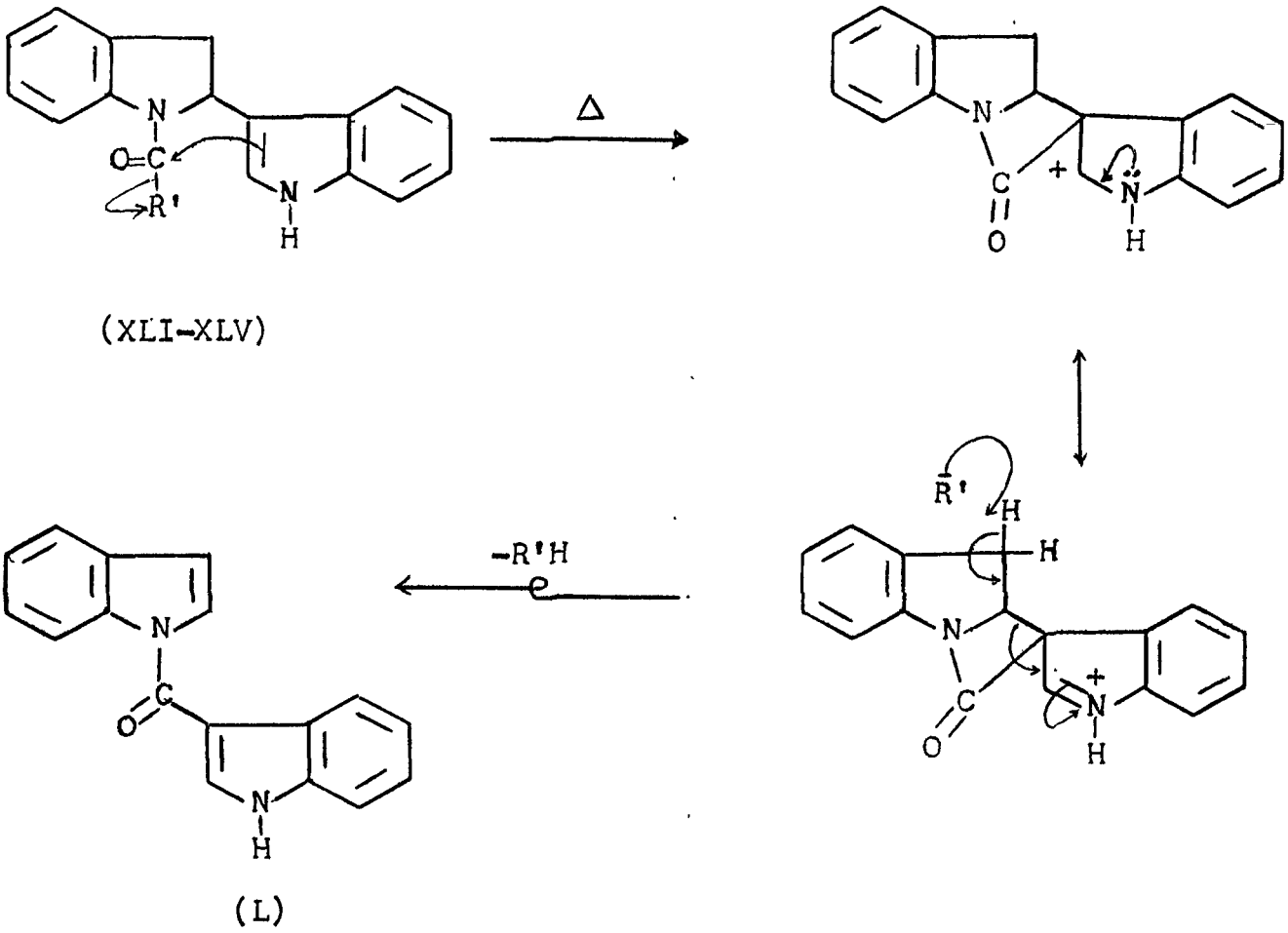
A further study of the driving force that makes compound (XXXVIII) change to a more stable product (L) even at room temperature has been undertaken. The compound (XXXVIII) and its derivatives(XLI-XV) were either on direct heating or in the presence of a solvent smoothly transformed to 1,3'-carbonyl biindole (L).



	R'
(XLI)	$NHCH_3$
(XLII)	$N(CH_3)_2$
(XLIII)	NHC_2H_5
(XLIV)	$N(C_2H_5)_2$
(XLV)	$NHCH_2Ph$

(L)

This transformation involved a novel type of rearrangement in which the indole system migrates to the carbonyl carbon. The mechanism for the transformation (XXXVIII, XLI-XLV) has been outlined below:



(XLI-XLV)

(L)

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ALIGARH, U.P., INDIA

*Ref. No.*_____ *Date* June 1, 1986

This is to certify that the work described in this thesis is the original work of the candidate and is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

(Dr. Abul Fazal)
Reader in Chemistry

Acknowledgement

I am immensely indebted to late Dr. Naseem Hasan Khan, my Research Supervisor, Reader, Department of Chemistry, Aligarh Muslim University, whose invaluable advice and guidance led to the development of the work embodied in this thesis.

I wish to express my great sense of gratitude to Dr. Abul Fazal, Reader, Department of Chemistry, Aligarh Muslim University, who acted as an immediate guide and has helped me in coming up of this thesis. I owe an enormous debt to him for his sincere advice, helpful suggestions and sympathetic attitude towards me.

I extend my heartfelt thanks to Prof. M.S. Ahmad, Chairman, Department of Chemistry, for providing necessary research facilities.

I remain beholden to my senior colleague, Dr. Mubarak Husain, for his cooperation, useful discussions and his keen interest in every stage of this thesis. Thanks are also due to my other research colleagues for their help and cooperation.

I express my sincere regards to my revered parents for their sacred love and good wishes which have been a great source of inspiration to me.

Financial assistance from Council of Scientific and Industrial Research (New Delhi) is acknowledged.

Mashkoor Husain

(Mashkoor Husain)

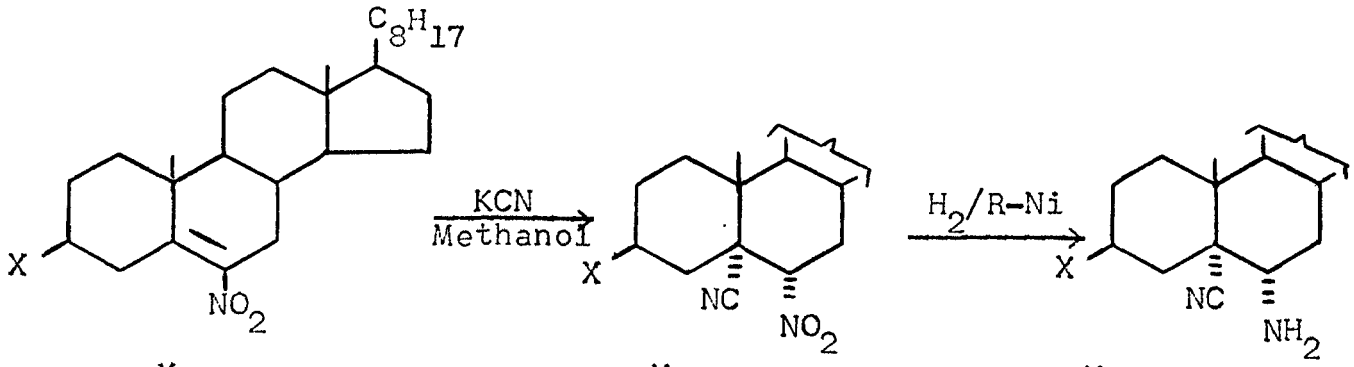
Contents

Summary

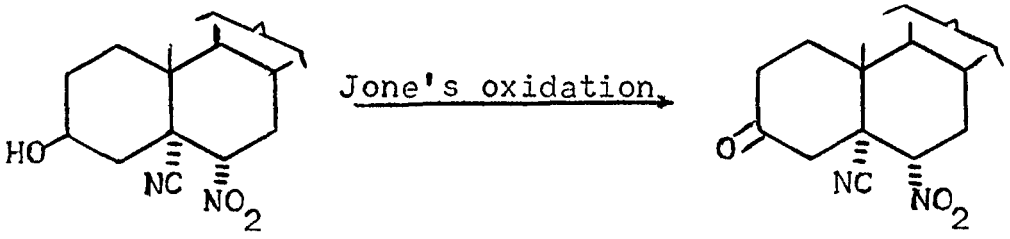
PART-1

Synthesis of steroidal cyanoamines

This section deals with the preparation of steroidal cyanoamines. Nitroolefins were treated with KCN in methanol to obtain nitrocyanides (V-VIII) and were subjected to hydrogenation in the presence of Raney-nickel as catalyst. 3β-Hydroxy-5-cyano-6α-nitro-5α-cholestane (V) on reduction with H_2/Ni gave 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (IX) and 5-cyano-6α-nitro-5α-cholestane (VII) on similar reduction provided 5-cyano-6α-amino-5α-cholestane (X). Acetoxy analogue (VI) gave product (IX) and 3β-chloroanalogue (VII) provides amine (X). Compound (XI) was obtained by the treatment of nitrocyanide (V) with Jone's reagent.

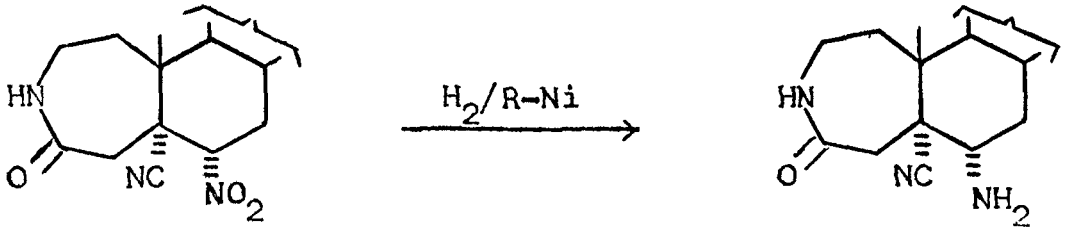


	X		X		X
(I)	-OH	(V)	-OH	(IX)	-OH
(II)	-OAc	(VI)	-OAc	(X)	-H
(III)	-H	(VII)	-H		
(IV)	-Cl	(VIII)	-Cl		



(V) (XI)

The nitrolactam nitriles (XII) and (XIII) obtained by the reaction of 5-cyano-6α-nitro-5α-cholestan-3-one (XI) with an excess of hydrazoic acid, when reduced with H_2/Ni provided the respective amines (XIV) and (XV) in the excellent yields. The lactam and nitrile function did not get affected during the hydrogenation.



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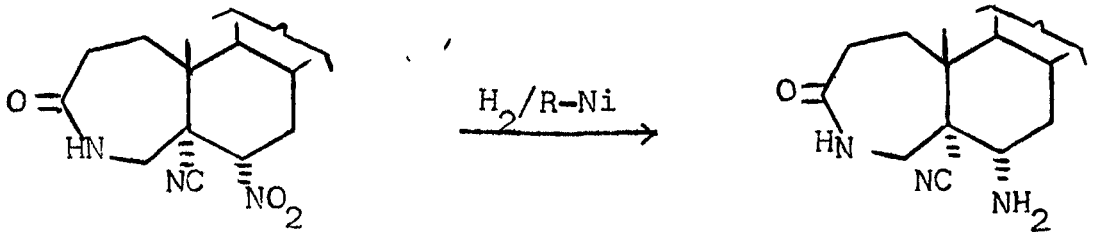
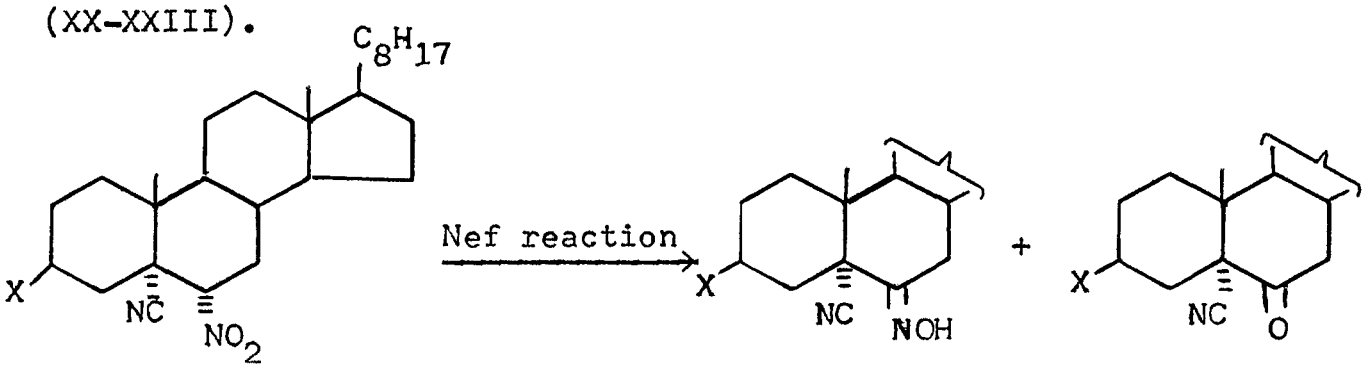


(XIII) (XV)

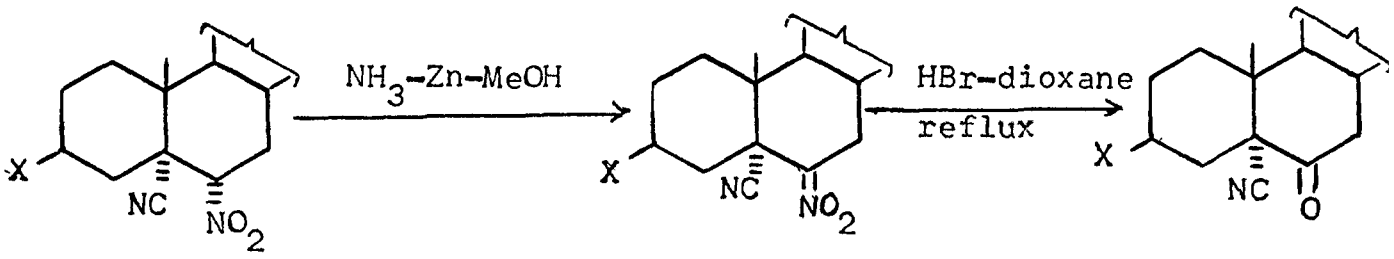
PART-2

Synthesis of steroidal α-cyanoketones

Nef reaction of 5-cyano-6α-nitro-5α-cholestane (V-VIII) has been undertaken in order to synthesise 5 -cyano-5α-cholestan-6-ones (XX-XIII). This reaction provided a mixture of respective cyanoketone and cyanooxime. Acetoxy analogues(XXI and XVII) were not obtained due to the alkaline conditions of the reaction. Nitrocyanides (V-VIII) on treatment with $Zn-NH_3$-MeOH reagent, were selectively transformed to the above cyanooximes (XVI-XIX) respectively in good yields. The oximes (XVI-XIX) were then hydrolysed with HBr in dioxane to their respective cyanoketones (XX-XXIII).

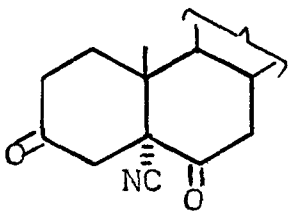


	X		X		X
(V)	-OH	(XVI)	-OH	(XX)	-OH
(VII)	-H	(XVIII)	-H	(XXII)	-H
(VIII)	-Cl	(XIX)	-Cl	(XXIII)	-Cl



	X		X		X
(V)	-OH	(XVI)	-OH	(XX)	-OH
(VI)	-OAc	(XVII)	-OAc	(XXI)	-OAc
(VII)	-H	(XVIII)	-H	(XXII)	-H
(VIII)	-Cl	(XIX)	-Cl	(XXIII)	-Cl

The cyanoketone (XX) and cyanooxime (XVI) when treated with Jone's reagent, afforded 5-cyano-5α-cholestane-3,6-dione (XXIV) and 5-cyano-6-oximino-5α-cholestan-3-one (XXV).



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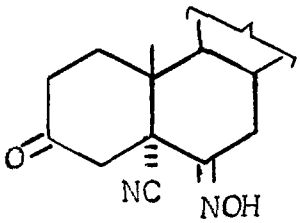
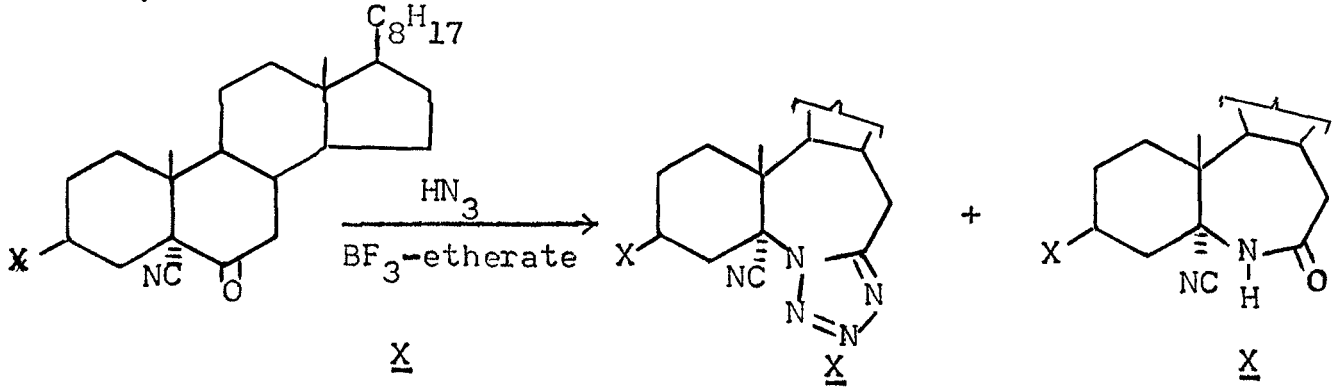


(XXV)

PART-3

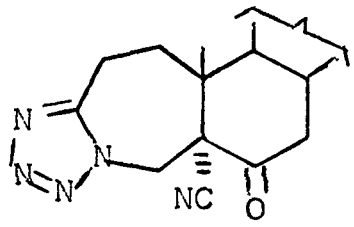
Synthesis of cyano-azasteroids

It describes the preparation of azasteroids (tetrazoles and lactams) from hitherto unreported cyanoketones (XX-XIV). The 3β-substituted 5-cyano-5α-cholestan-6-ones (XX-XXIII) on reaction with hydrazoic acid and borontrifluoride-etherate, provided the respective 6-aza tetrazoles (XXVI-XXIX) and 6-aza lactams (XXX-XXXII) in case of 3β-acetoxy-5-cyano-5α-cholestan-6-one (XXI), only tetrazole (XXVII) was obtained.



	X		X		X
(XX)	-OH	(XXVI)	-OH	(XXX)	-OH
(XXI)	-OAc	(XXVII)	-OAc		
(XXII)	-H	(XXVIII)	-H	(XXXI)	-H
(XXIII)	-Cl	(XXIX)	-Cl	(XXXII)	-Cl

Cyanodiketone (XXIV) when treated with hydrazoic acid and borontrifluoride etherate under the Schmidt reaction condition afforded 4-aza-A-homo-5-cyano-6-oxo-5α-cholestano[4,3-d] tetrazole (XXXIII), 3,6-diaza-A,B-bishomo-5-cyano-5α-cholestano [3,4-d][6,7-d]bistetrazole (XXXIV) and 3,6-diaza-A,B-bishomo-7-oxo-5-cyano-5α-cholestano[3,4-d]tetrazole (XXXV).



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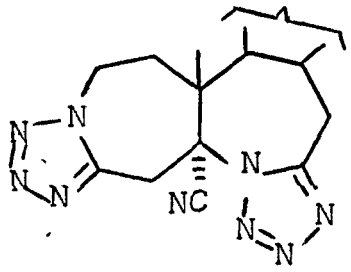

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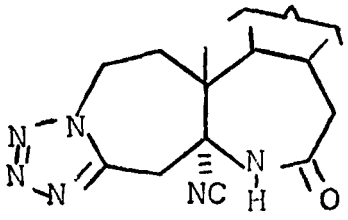
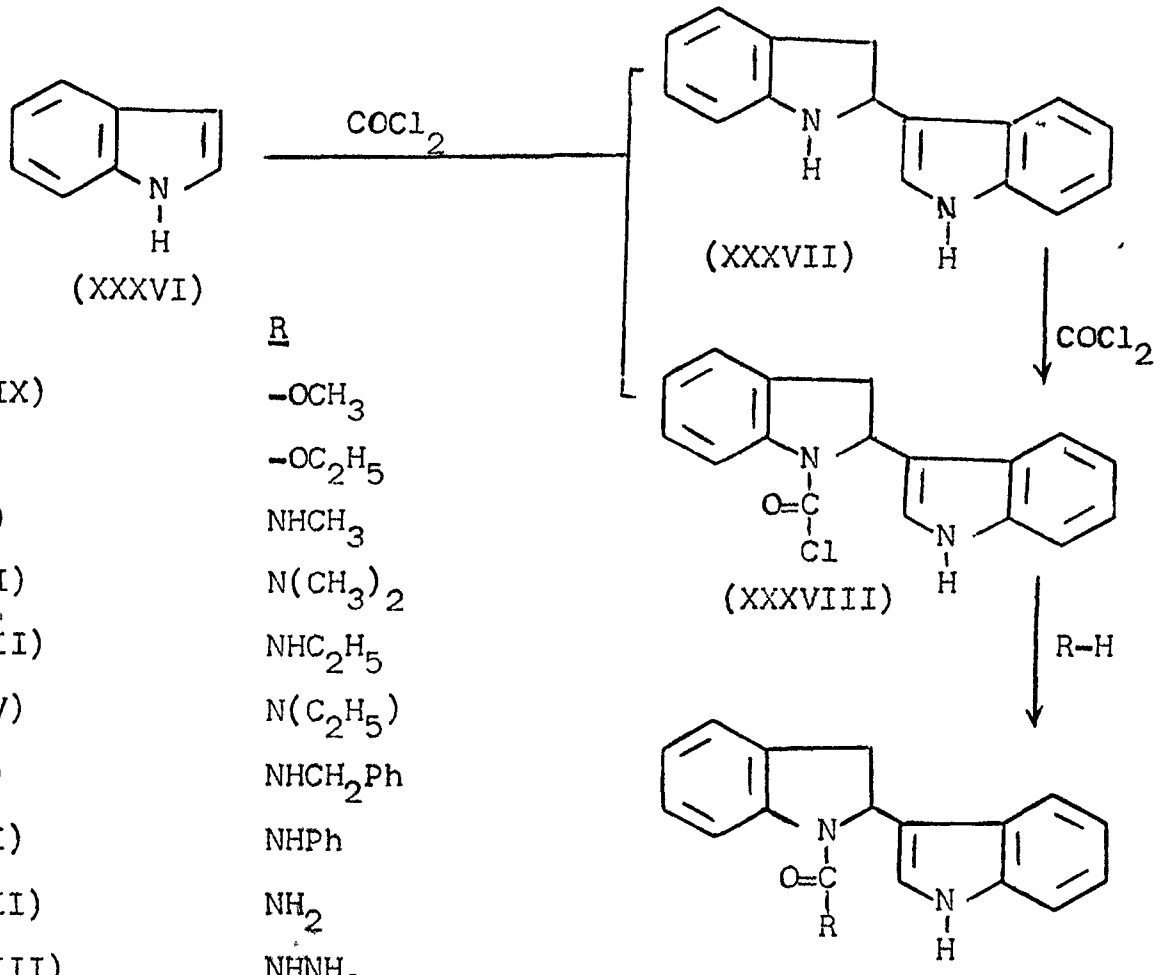


(XXXV)

PART-4

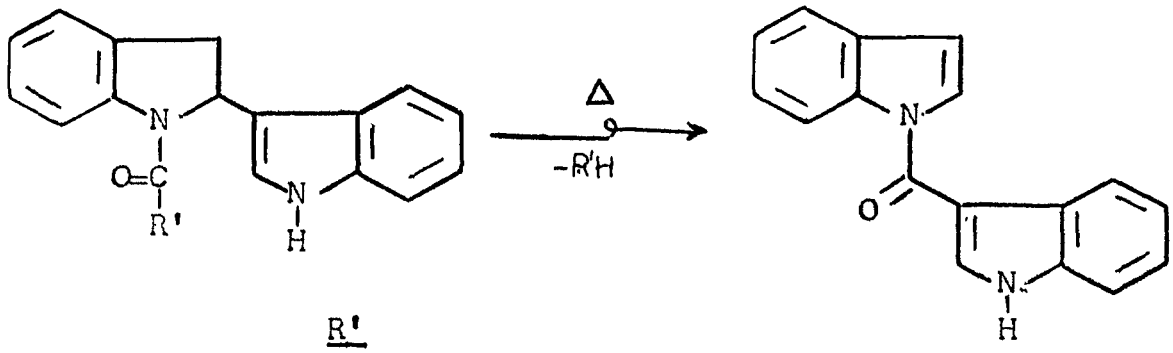
Synthesis of indole dimers

This part describes the synthesis of 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (XXXVII) by the reaction of indole (XXXVI) with phosgene. The derivatives (XXXIX-XLIX) have been obtained by the reaction of the former with respective reagents. The indole dimer (XXXVII) when treated with phosgene also produced the carbonyl chloride (XXXVIII).



	R
(XXXIX)	$-OCH_3$
(XL)	$-OC_2H_5$
(XLI)	$NHCH_3$
(XLII)	$N(CH_3)_2$
(XLIII)	NHC_2H_5
(XLIV)	$N(C_2H_5)$
(XLV)	$NHCH_2Ph$
(XLVI)	NHPh
(XLVII)	NH_2
(XLVIII)	$NHNH_2$
(XLIX)	CN

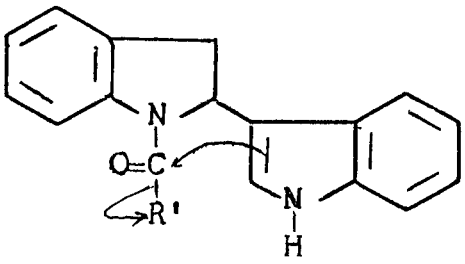
A further study of the driving force that makes compound (XXXVIII) change to a more stable product (L) even at room temperature has been undertaken. The compound (XXXVIII) and its derivatives(XLI-XV) were either on direct heating or in the presence of a solvent smoothly transformed to 1,3'-carbonyl biindole (L).



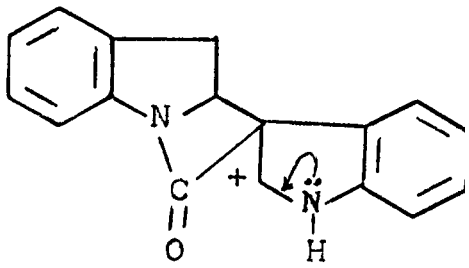
	R'
(XLI)	$NHCH_3$
(XLII)	$N(CH_3)_2$
(XLIII)	NHC_2H_5
(XLIV)	$N(C_2H_5)_2$
(XLV)	$NHCH_2Ph$

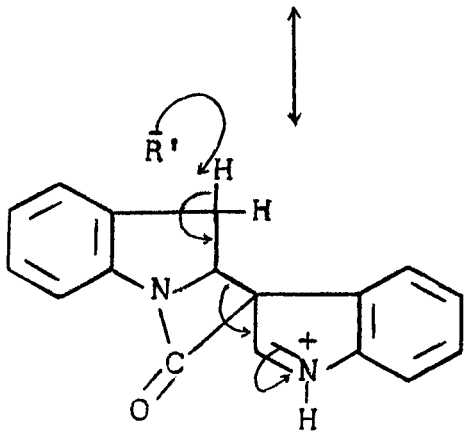
(L)

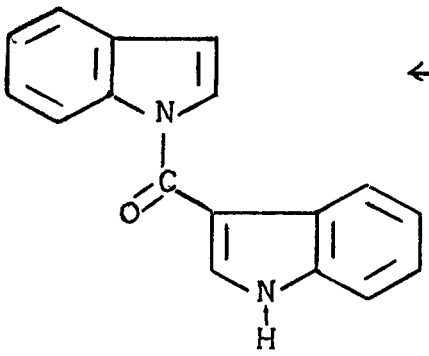
This transformation involved a novel type of rearrangement in which the indole system migrates to the carbonyl carbon. The mechanism for the transformation (XXXVIII, XLI-XLV) has been outlined below:



(XLI-XLV)







(L)

Introduction

Nitrogenous compounds form a major part of the organic compounds which are introduced into the chemical literature through day to day researches. The preparation of these compounds has a motivation among the chemists not only because nitrogen containing compounds are generally associated with various kinds of biological properties but also because they have found a wide application in industries as well. Notable among these compounds are antibiotics, such as penicillins, antimalarials like quinine and its other derivatives, and some of the vitamins etc., which have acquired the fundamental and indispensable importance in the modern medical treatment against many diseases. Amino acids and peptides are responsible for most of the essential metabolic process in the living organisms including man. Polymers obtained from acrylonitrile, ϵ-caprolactams and urethanes are the most utilized nitrogenous chemicals in the polymer industries throughout the world. Moreover, this field of research is expanding and provides impetus and incentives to the investigator involved in the exploration of nitrogenous compounds.

With the realization of their diverse uses, synthesis of steroidal cyanoamines, cyanoaminolactams, cyanoketones, cyanotetrazoles and various substituted indole dimers has been undertaken in this thesis.

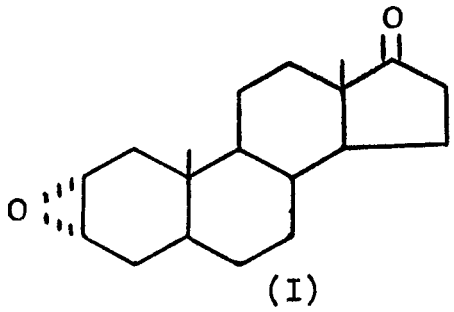
Part One

Steroidal Cyanoamines

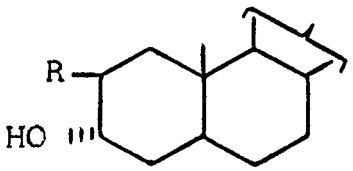
Theoretical

Synthesis of aminosteroids has drawn the attention of chemists for the last so many years due to their some interesting biological activities[1-6]. Steroidal amines have been reported to possess tranquilising, anticonvulsant, antiarrythmic anaesthetic and other activities. A number of methodologies have been developed to prepare steroidal amines differing in the position of amino group and with other functionalities.

Hewett et al.[7] synthesised steroidal amines by the condensation of epoxyandrostanes with primary and secondary amines. They treated 2α, 3α and 2β, 3β-epoxy-5α-androstanes (I and III) with amines which afforded the corresponding amino alcohols (IIa-f and IVa-f).



(I)



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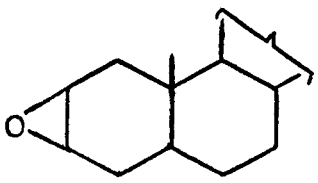

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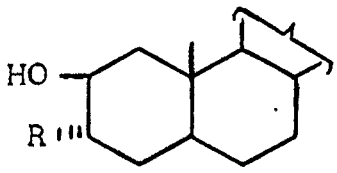
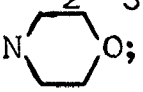
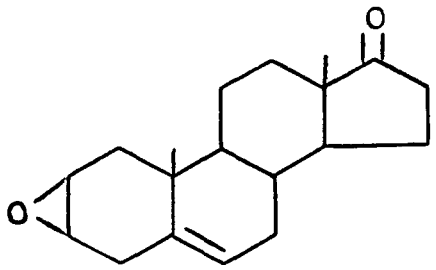


(IV)

R= (a) $-NH-CH_3$; (b) $-NHCH_2CH_3$; (c) $-N(CH_3)_2$;
(d) $-N(C_2H_5)_2$; (e)  ; (f) 

Various other steroidal aminoalcohols[8-11] were also synthesised by the transdiaxial ring opening of different steroidal epoxides with amines.

Campbell et al.[12] obtained azidoalcohols by the reaction of 2β,3β-epoxyandrost-5-en-17-one (V) and its 2α,3α-epimer (VIII) with sodium azide. These azidoalcohols (VI and IX) on subsequent reduction with $LiAlH_4$ gave 3α-amino-2β-hydroxyandrost-5-en-17-one (VII) and 2β-amino-3α-hydroxyandrost-5-ene-17-one (X).



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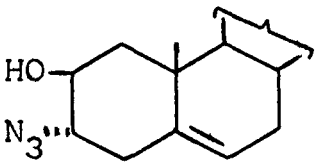

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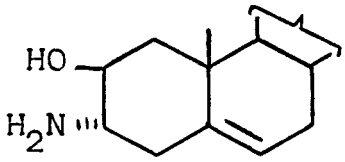

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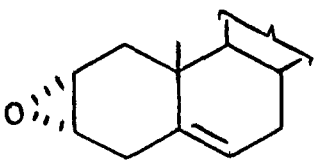

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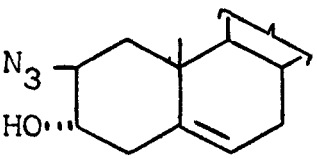

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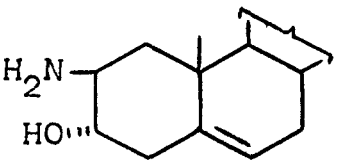
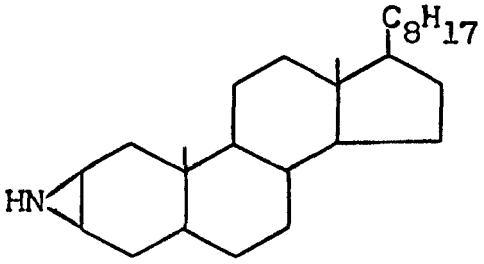


(X)

Hassner and Heathcock[13] prepared aminoalcohols via transdiaxial ring opening of aziridines. As 2β,3β-iminocholestane

(XI) on treatment with acetic acid afforded 2β-amino-3α-hydroxy-5α-cholestane (XII) in 90% yield.



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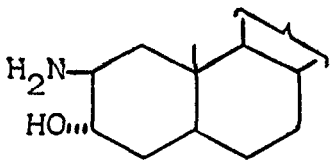
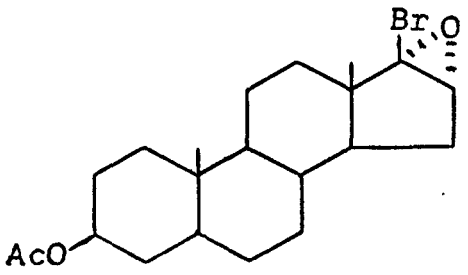
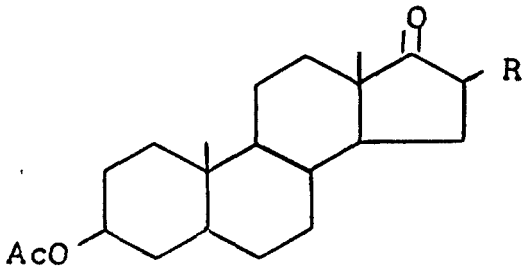


(XII)

Hassner and Catsoulacos[14] treated steroidal bromo-epoxides with primary and secondary amines at room temperature to obtain amino ketones; 3β-acetoxy-16α,17α-epoxy-17-bromo-5α-androstane (XIII) on treatment with isopropyl amine, diethyl amine and morpholine gave amino ketones (XIVa-c).



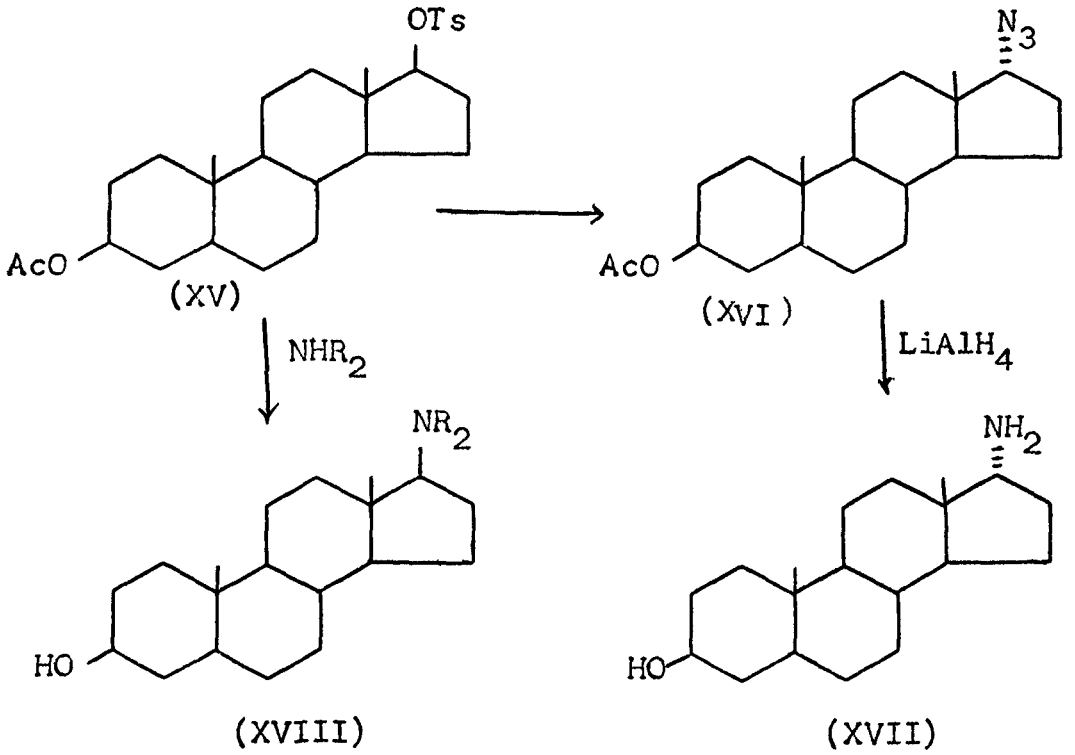
(XIII)



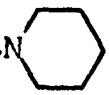
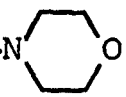
(XIV)

R= (a) $-NHCH(CH_3)_2$; (b) $-N(C_2H_5)_2$; (c)  etc.

Davis et al.[15] prepared 17α-aminoandrostane (XVII) from (XV). Treatment of 3β-acetoxy-17β-tosyloxy-5α-androstane(XV) with sodium azide resulted 17α-azide (XVI), which was reduced with Lithium aluminium hydride to amine (XVII). Whereas 17β-tosylate (XV) on reaction with various amines gave substituted steroidal amines (XVIIIa-d).

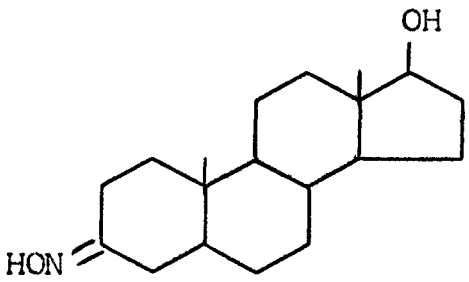


(XVIII) (XVII)

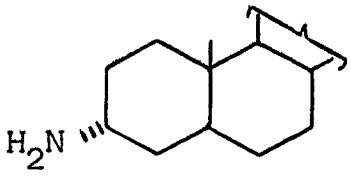
NR_2= (a) $-NMe_2$; (b)  ; (c)  ; (d) 

Yagi et al.[16] treated 3-oximino-5α-androstane-17β-ol (XIX) with sodium and n-propyl alcohol to afford 3α-amino-5α-

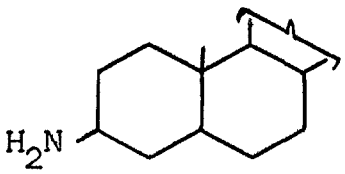
androstan-17β-ol (XX) in good yield while catalytic reduction of the oxime yielded the 3β-amino-5α-androstan-17β-ol (XXI). These amines were further converted to various amino derivatives.



(XIX)

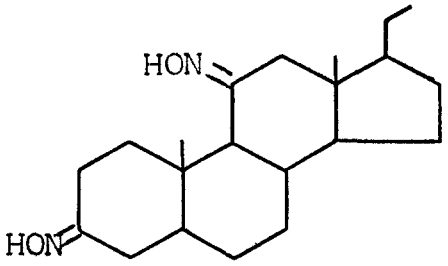


(XX)



(XXI)

Campbell et al.[17] prepared four isomeric 3,11-diamino-5α-pregnanes (XXIII-XXVI) through the reduction of dioxime (XXII) using different reducing agents and varying reaction conditions.



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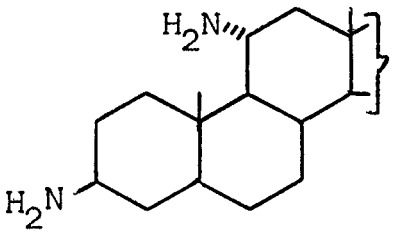
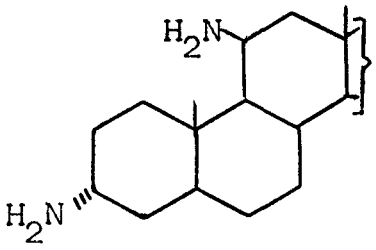
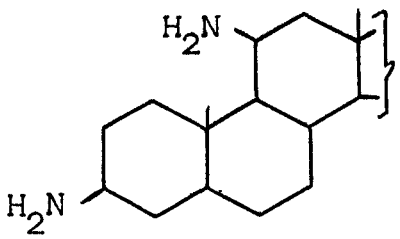


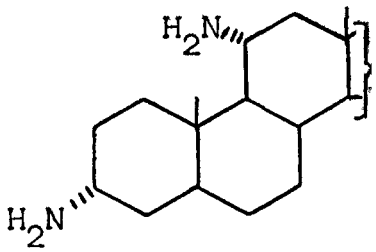
(XXIII)



(XXIV)

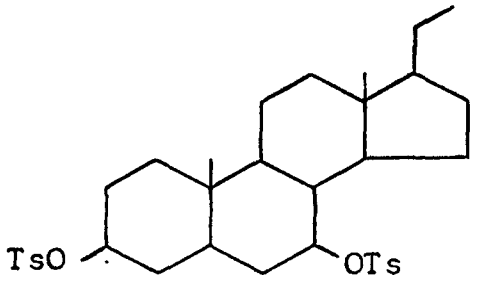


(XXV)

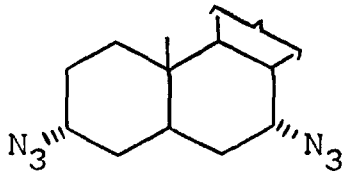


(XXVI)

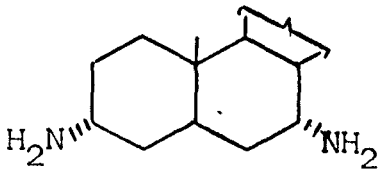
Campbell et al.[18] synthesised 3,7-diamino-5α-pregnane (XXIX) from 3β,7β-dihydroxy-5α-pregananeditosylate (XXVII). Ditosylate (XXVII) on reacting with sodium azide converted to 3α,7α-diazido-5α-pregnane (XXVIII), which on reduction with $LiAlH_4$ afforded 3α,7α-diamino-5α-pregnane (XXIX). The diamine was converted to various derivatives by standard known procedures.



(XXVII)

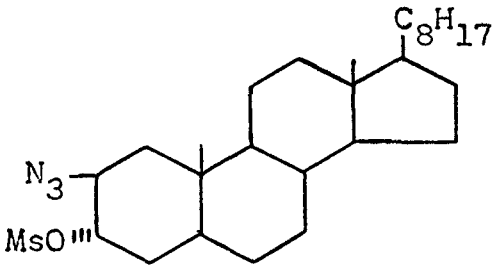


(XXVIII)

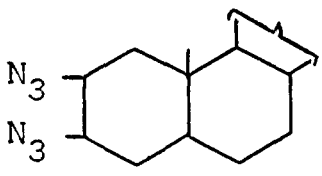


(XXIX)

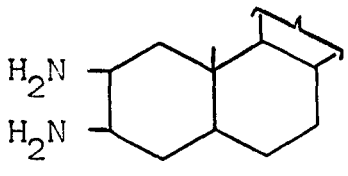
Ponsold and Klem[19] prepared 2α, 3α and 2β, 3β-diamino-cholestanes (XXXII and XXXV)[20] and their derivatives from the corresponding transdiaxial azidoalcohol mezylates (XXX and XXXIII) via the cis diazides (XXXI and XXXIV).



(XXX)



(XXXI)



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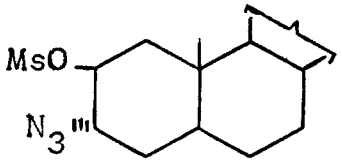
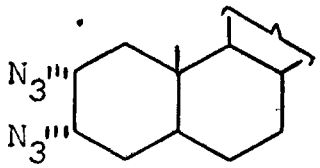


(XXXIII)



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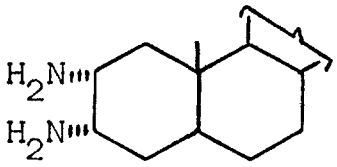
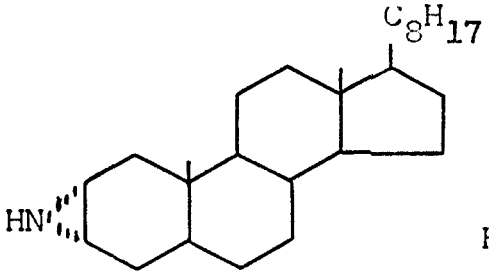


(XXXV)

2β,3α-Diaminocholestane (XXXIX)[19] is prepared by ring opening of 2α,3α- and 2β,3β-iminocholestane (XXXVI and XI) with sodium azide and subsequent reduction of the obtained azidoamines (XXXVII and XXXVIII) with $LiAlH_4$.



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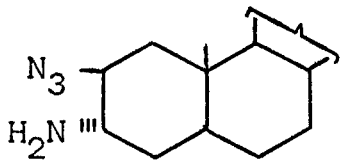
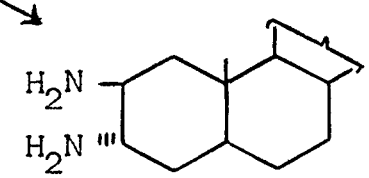
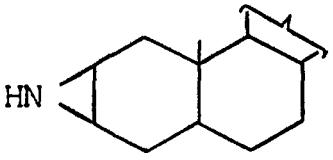


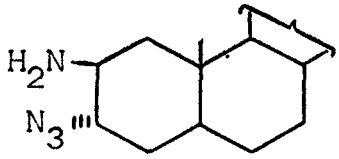
(XXXVII)



(XXXIX)

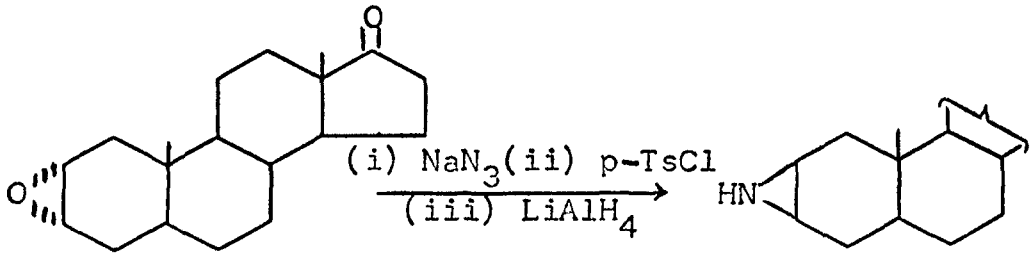


(XI)

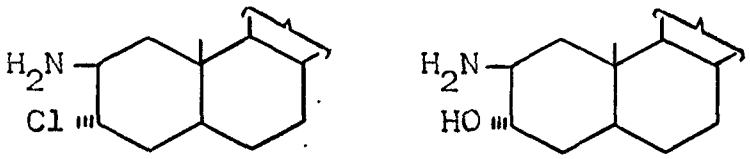


(XXXVIII)

Ponsold and Preibsch[21] have synthesised steroidal chloroamine (XLII)[22] and aminoalcohol (XLIII) from epiminopregnenone (XLI), prepared from epoxide (XL) via azidoalcohol tosylates.

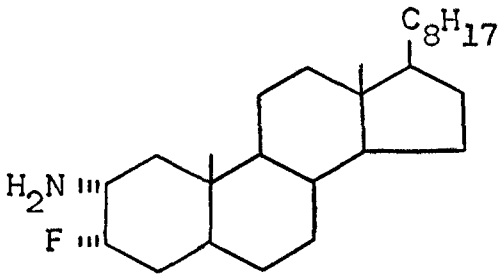


(XL) (XLI)

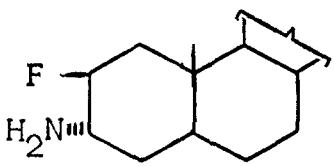


(XLII) (XLIII)

Recently[23] fluoroaminocholestanes (XLIV and XLV) were also synthesised by the treatment of isomeric 2,3-epiminocholestanes with Olah's reagent (HF in pyridine).



(XLIV)



(XLV)

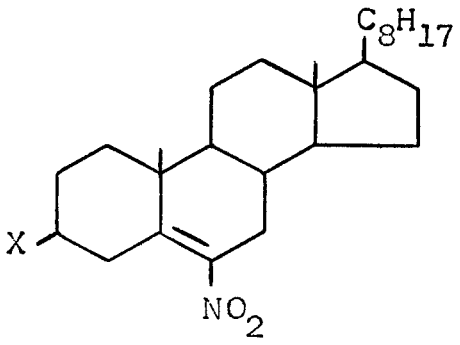
Discussion

Steroidal amines have become of interest in recent years because of the discovery of biological activity associated with a number of aminosteroids and also because of their use as potential drugs. As a result of this realization, synthesis of steroidal amines became a matter of much importance and consequently a number of papers appeared for the preparation of aminosteroids, which prompted us to undertake the synthesis of steroidal cyanoamines by the catalytic hydrogenation of steroidal nitrocyanides.

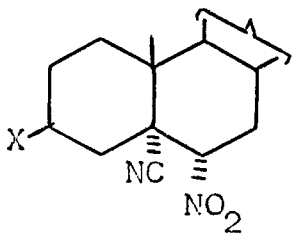
Preparation of steroidal cyanoamines

Steroidal nitrocyanides (L-LIII) prepared by the reaction of corresponding nitroolefins with KCN in methanol, were subjected to hydrogenation in the presence of Raney-nickel as catalyst. This reduction afforded cyanoamines (LIV and LV). The acetate group hydrolysed to hydroxy in case of substrate (LI) whereas dechlorination occurred during the reduction of (LIII).

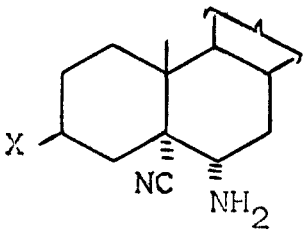
The nitrocyanide (L) when treated with Jone's reagent to get its 3-oxo analogue (LVI) which in turn subjected to reaction with hydrazoic acid and borontrifluoride etherate to obtain isomeric lactams (LVII and LVIII). These lactams when reduced with H_2/Ni, produced the respective cyanoaminolactams (LIX and LX) in good yields.



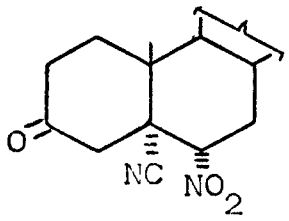
X	
(XLVI)	-OH
(XLVII)	-OAc
(XLVIII)	-H
(XLIX)	-Cl



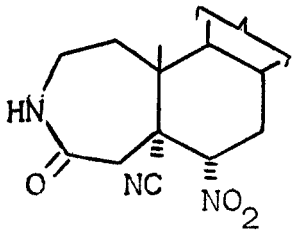
X	
(L)	-OH
(LI)	-OAc
(LII)	-H
(LIII)	-Cl



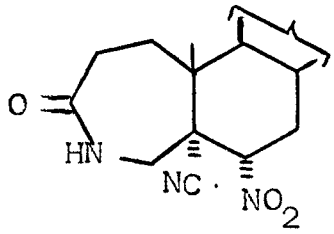
X	
(LIV)	-OH
(LV)	-H



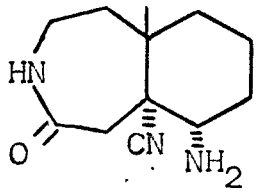
(LVI)



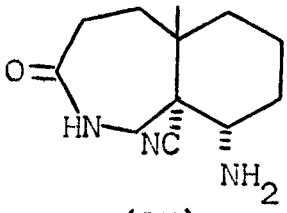
(LVII)



(LVIII)



(LIX)

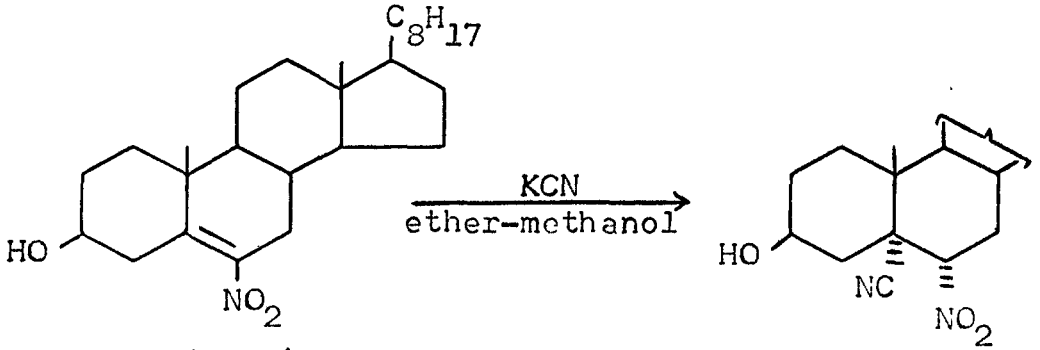


(LX)

Reaction of 3β-hydroxy-6-nitrocholest-5-ene (XLVI) with KCN

The reaction of compound (XLVI) with potassium cyanide was carried out by pouring a solution (in methanol-ether mixture)

of the substrate over KCN in excess. At the completion of reaction, the reaction mixture worked up and a compound, which melted at 140°, was obtained.



(XLVI) (L)

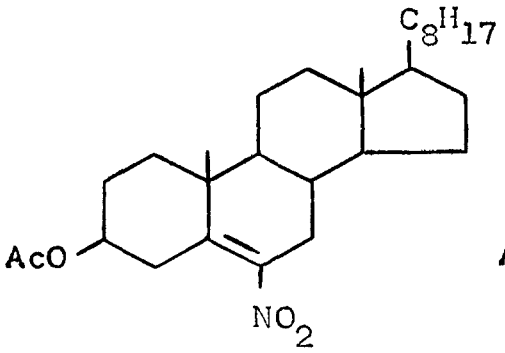
Characterization of the compound, m.p.140°, as 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L)

The compound, m.p.140°, analysing for $C_{28}H_{46}N_2O_3$ suggested the formation of nitrocyanide (L). Its IR spectrum showed absorption bands at 3420 for OH and 2250 cm^{-1} for C≡N groups. Bands at 1560 and 1370 cm^{-1} are compatible with saturated NO_2 stretching frequencies. The PMR spectrum of this product exhibited a multiplet at δ 4.55 with W1/2=17 Hz for one proton indicated the C6-proton to be axial (β-oriented and consequently the nitro group as equatorial). Had this proton[24] been equatorial (α-oriented), it could have been observed as a narrow triplet with

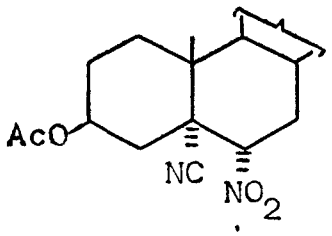
J= 3 Hz. Moreover, the α-nitro at C6 is preferred over its β-analogue because in the latter case, 1,3-diaxial interaction between C10-methyl and C6-β-nitro would be unfavourable. Another multiplet with W1/2=18 Hz appearing at δ 3.97 for 1H is due to the C3-axial proton. This half-band width indicated the ring junction A/B to be trans. A one-proton broad signal at δ 3.20 which disappeared on shaking with D_2O could be assigned to the OH proton. Angular methyls were observed at δ 1.07 (C10-CH_3), 0.67 (C13-CH_3), 0.92 and 0.82 (remaining methyl protons).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVII) with KCN

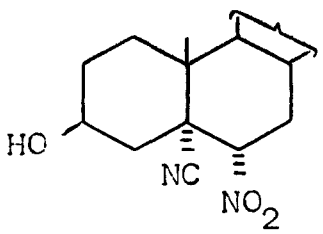
The reaction of substrate (XLVII) with KCN carried out in a similar way, furnished two products, melting at 213° and 140°.



(XLVII)



(LI)



(L)

Characterization of the compound, m.p.213° as 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI)

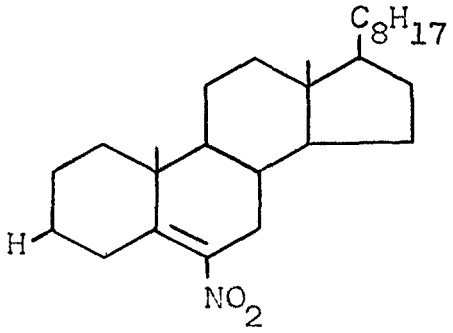
The compound, m.p.213°, giving an analysis for $C_{30}H_{48}N_2O_4$ suggested the formation of nitrocyanide (LI). In its IR spectrum, absorption bands observed at 2245, 1740, 1565 and 1370 cm^{-1} are compatible with C≡N, $OCOCH_3$, and saturated NO_2 functional groups respectively. PMR spectrum of this compound showing a multiplet with W1/2=19 Hz at δ 5.30 for one proton is ascribable for C3-αH (A/B trans). Another multiplet for one proton (C6-H) having a half-band width of 19 Hz and appearing at δ 4.73 confirms the orientation of proton at C6 as axial. A sharp singlet for 3 protons seen at δ 2.01 is due to the acetate protons at C3. Methyl protons were observed at δ 1.10 (C10-CH_3), 0.70 (C13-CH_3), 0.95 and 0.85 (remaining methyl protons).

Characterization of the compound, m.p.140°, as 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L)

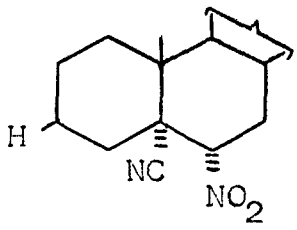
This compound was characterized as 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane on the basis of its identity (m.p., m.m.p., co-TLC and IR) with the authentic sample (L). Further confirmation of this structure came from its smooth conversion to the acetoxy analogue (LI) on its reaction with acetic anhydride and pyridine.

Reaction of 6-nitrocholest-5-ene (XLVIII) with KCN

The compound (XLVIII) on reaction with potassium cyanide under the conditions as described earlier, afforded a compound, m.p.160°.



(XLVIII)



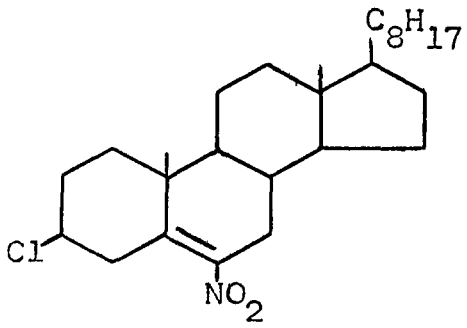
(LII)

Characterization of the compound, m.p.160°, as 5-cyano-6α-nitro-5α-cholestane (LII)

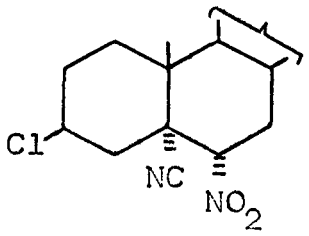
The compound, m.p.160° (reported[63] m.p.161°) showed in its IR spectrum absorption bands at 2245 and 1560, 1390 cm^{-1} which correspond to C≡N and saturated NO_2 functional groups respectively. PMR spectrum showing a multiplet at δ 4.50 with W1/2=16 Hz integrating for one proton (C6-H) suggested this proton to be axial and consequently the nitro group as equatorial. The assignment of ring junction A/B as trans in this product was made analogous to that in the case of 3β-substituted products (L, LI, LIII). Methyl protons were seen at δ 1.00, 0.95, 0.85 and 0.65.

Reaction of 3β-chloro-6-nitrocholest-5-ene (XLIX) with KCN

The reaction of the substrate (XLIX) with KCN in a similar way furnished a compound, m.p.143°.



(XLIX)



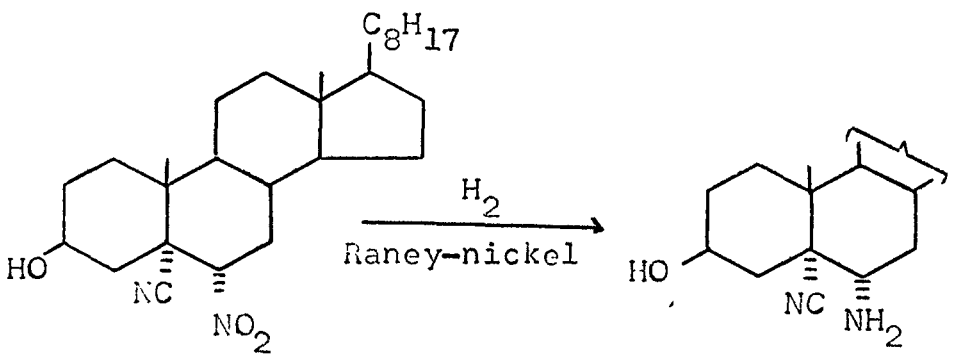
(LIII)

Characterization of the compound, m.p.143°, as 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII)

The compound, m.p.143° ($C_{28}H_{45}N_2OCl$; showing positive Beilstein test for the presence of halogen) gave absorption bands in its IR spectrum at 2240, 1560, 1380 and 780 cm^{-1} for C≡N, NO_2 and C-Cl stretching frequencies. PMR spectrum exhibiting a multiplet (W1/2=18 Hz) at δ 4.50 for C6-βH and another multiplet (W1/2=18 Hz) appearing at δ 4.20, integrating for one proton (C3-α<u>H</u>) confirm the A/B ring junction to be trans. Consequently the cyano group at C5 is α-oriented. Methyl signals appeared at δ 1.0, 0.90, 0.75 and 0.67.

Hydrogenation of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L) using Raney-nickel as the catalyst

Nitrocyanide (L) when subjected to hydrogenation in the presence of an excess of Raney-nickel (specific and selective catalyst)[25] at a hydrogen pressure of 30 psi, provided a product, m.p.185°.



(L) (LIV)

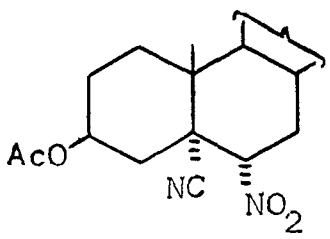
Characterization of the compound, m.p.185°, as 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (LIV)

The compound, m.p.185°, showed molecular composition as $C_{28}H_{48}N_2O$, which indicated the formation of a cyanoamine. Its IR spectrum displayed absorption bands at 3410 and 3350, 3300 cm^{-1} corresponding to OH and NH_2 functions respectively. A medium sharp band at 2235 cm^{-1} for C≡N stretching and the absence of bands at 1550-1570 cm^{-1} in its IR spectrum confirms the selective

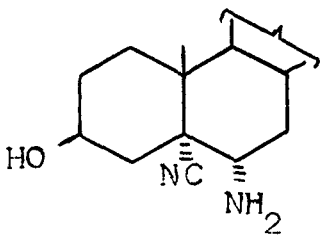
reduction of nitro group into an amine and that C≡N group remained unaffected[26]. Bands at 1620 and 900 cm^{-1} are compatible with NH-bending vibrations. The PMR spectrum of this compound exhibiting a multiplet at δ 4.0 (Wl/2=19 Hz) for one proton (C3-α<u>H</u>) suggested that the ring junction of ring A and B as trans. A broad signal for one proton at δ 3.40 which disappeared on shaking with D_2O is ascribable for C3-O<u>H</u> proton. Another multiplet (Wl/2=24 Hz) centred at δ 2.80 for one proton is due to the C6-βH. NH_2 protons were found to be merged with the methylene protons (an area of 2 protons was found to be exchangeable with D_2O in methylene envelope). Methyl protons were seen at δ 0.95, 0.90, 0.81 and 0.65.

<u>Hydrogenation of 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI) using Raney-nickel as the catalyst</u>

The catalytic hydrogenation of the compound (LI) in the presence of Raney-nickel at 30 psi furnished a product, melting at 185°.



(LI)



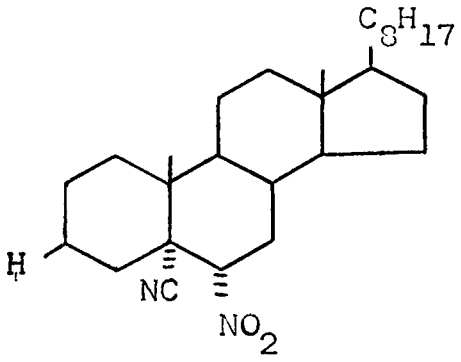
(LIV)

Characterization of the compound, m.p.185° as 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (LIV)

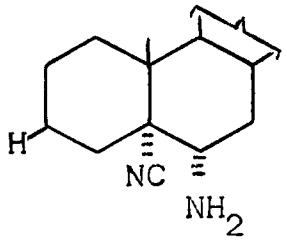
The product, melting at 185° was found to be identical with 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (LIV) obtained from the reaction of (L) with H_2/Ni in all respects (m.p., m.p.p., co-TLC and IR).

Hydrogenation of 5-cyano-6α-nitro-5α-cholestane (LII) using Raney-nickel

The substrate (LII) on reduction with hydrogen in the presence of Raney-nickel at 30 psi provided a product, m.p.120°.



(LII)



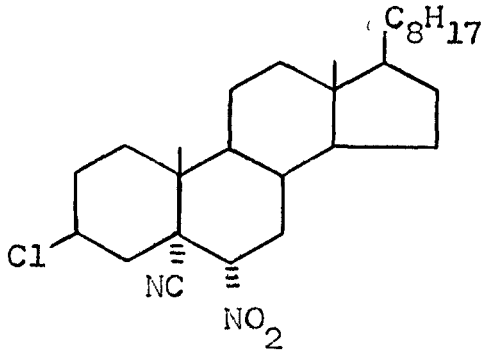
(LV)

Characterization of the compound, m.p.120°, as 5-cyano-6α-amino-5α-cholestane (LV)

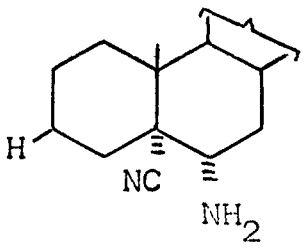
The compound melting at 120° was analysed for $C_{28}H_{48}N_2$. The IR spectrum of this compound showed absorption bands at 3395, 3350 cm^{-1} for NH_2 function. A medium sharp band at 2240 cm^{-1} was due to C≡N stretching. Absence of a band in 1550-1570 cm^{-1} and appearance of bands at 1620 and 880 cm^{-1} evidenced the formation of amine. The structure (LV) assigned to this product was supported by the PMR spectrum which exhibited a multiplet (W1/2=22 Hz) for one proton centred at δ 2.75. This half-band width clearly shows α-orientation for the NH_2 group at C6. NH_2 protons were found to be merged with the methylene protons (two protons in the methylene envelope at δ 2.00, were found to be exchangeable with D_2O). The junction of rings A and B was assigned as trans analogous to 3β-substituted product (LIV). Methyl protons were observed at δ 0.95 (C10-CH_3), 0.68 (C13-CH_3), 0.93 and 0.83 (remaining methyl protons).

Hydrogenation of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII) using Raney-nickel as the catalyst

A similar hydrogenation of compound (LIII) with hydrogen and Raney-nickel gave a product, melting at 120°.



(LIII)



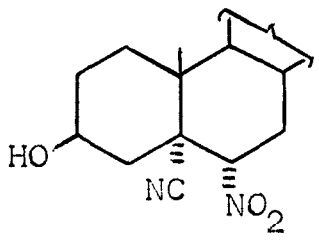
(LV)

Characterization of the compound, m.p.120° as 5-cyano-6α-amino-5α-cholestane (LV)

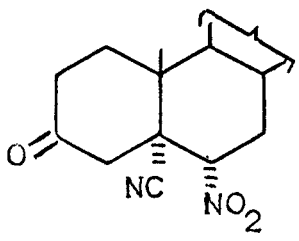
The product, m.p.120°, was found identical with 5-cyano-6α-amino-5α-cholestane obtained earlier from the reduction of (LII), in all respects.

Jone's oxidation of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L)

3β-Hydroxy-5-cyano-6α-nitro-5α-cholestane (L) was treated with Jone's reagent at 0-5°, when the reaction was over, the ethereal layer worked up in the usual way furnished a product melting at 155° (LVI).



(L)



(LVI)

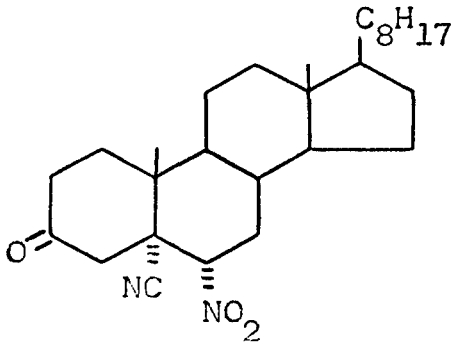
Characterization of the compound, m.p.155° as 5-cyano-6α-nitro-5α-cholestan-3-one (LVI)

The compound m.p.155° was analysed for $C_{28}H_{44}N_2O_3$. Its IR spectrum showing a strong absorption band at 1715 cm^{-1} confirmed the formation of ketone. Bands at 2245 and 1565, 1375 cm^{-1} are compatible with C≡N and NO_2 frequencies. Its PMR spectrum exhibited a multiplet with W1/2=20 Hz at δ 4.75 which is ascribable to the C6-β proton. Methyl signals were observed at δ 1.20, 0.98, 0.92 and 0.70.

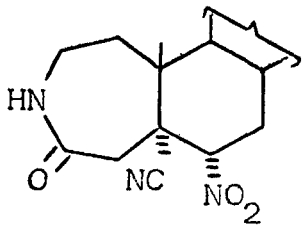
The above cyanoketone so obtained is of great importance as being suitable for synthetic modification on ring A by the use of suitable reagents.

Reaction of 5-cyano-6α-nitro-5α-cholestan-3-one (LVI) with hydrazoic acid using boron trifluoride etherate as the catalyst

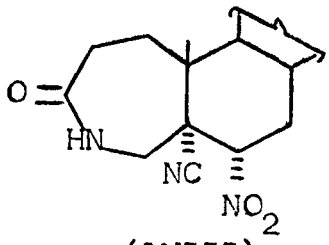
5-Cyano-6α-nitro-5α-cholestan-3-one (LVI) was kept with hydrazoic acid and borontrifluoride etherate at room temperature for 6 hrs. After usual work up and column chromatography two products, melting at 265° and 260° were obtained.



(LVI)



(LVII)



(LVIII)

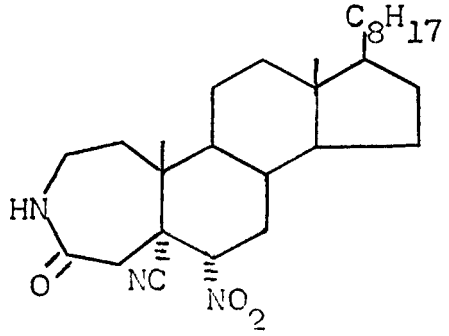
Characterization of the compound m.p.265° as 3-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-4-one (LVII) and the compound m.p.260° as 4-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-3-one (LVIII)

The products, m.ps.265 and 260° showed an analysis for $C_{28}H_{45}N_3O_3$. This analysis indicated the formation of lactams. Both products showing in their IR spectra a broad band at 3680-3375, 3550-3260 cm^{-1} and a strong band at 1675, 1670 cm^{-1} corresponding to NH and CO frequencies respectively further supported lactams (3-aza and 4-aza isomers). The presence of a medium sharp band at 2240 cm^{-1} indicated the non-participation of -CN group in reaction with hydrazoic acid. PMR spectra of these products helped in the distinction of the two isomers. A multiplet (which was not much affected by the addition of D_2O) at δ 3.30 integrating for 2 protons in the former, suggested the nitrogen insertion between C2 and C3 (3-aza), and a doublet like

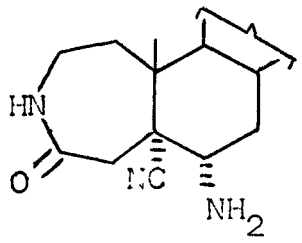
signal at δ 3.40 for 2H, which on D_2O shake simplified as a dist. doublet J=15 Hz, evidenced thepresence of NH adjacent to an isolated methylene group (C4a-2H) suggesting the nitrogen insertion between C3 and C4 (4-aza) in the latter compound. On the basis of this discussion, these products were identified as 3-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-4-one (LVII) and 4-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-3-one (LVIII) respectively. However, steroidal tetrazoles were not obtained in this reaction.

Hydrogenation of 3-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-4-one (LVII) using Raney-nickel as the catalyst

Nitrolactam (LVII) when subjected to reduction with H_2/Raney-nickel at 30 psi provided a compound, melting at 287-290° (LIX).



(LVII)



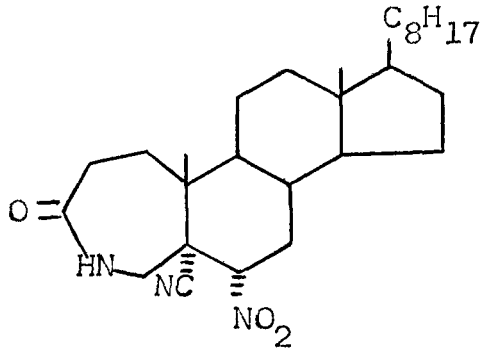
(LIX)

Characterization of the compound, m.p.287-290° as 3-aza-A-homo-5-cyano-6α-amino-5α-cholestan-4-one (LIX)

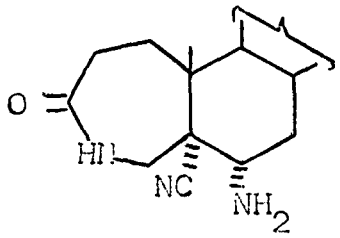
The compound, m.p.287-290°, analysing for $C_{28}H_{47}N_3O$ indicated the conversion of the nitro group into amine. The absence of absorption bands (IR spectrum) in the region 1570-1550 cm^{-1} ($-NO_2$) and appearance of additional bands in the region 3600-3200 cm^{-1} for NH_2 and 1670, 1650 cm^{-1} for CO stretching frequencies substantiated the formation of aminolactam. The presence of a sharp medium band at 2240 cm^{-1} for C≡N suggested that cyano group remained unaffected during the reduction. PMR spectrum showed no peaks in the region δ 4.5-4.8 ($C\underline{H}-NO_2$) whereas a multiplet centred at δ 2.2 for 2 protons found to be exchangeable with D_2O was assignable to $N\underline{H}_2$ protons. A broad signal at δ 6.60 for one proton (diminished on shaking with D_2O) was due to $N\underline{H}$-CO proton. Another multiplet observed at δ 3.60 for 2H which is ascribable to C2-protons, confirmed its structure as 3-aza-A-homo-5-cyano-6α-amino-5α-cholestan-4-one (LIX).

Hydrogenation of 4-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-3-one (LVIII) using Raney-nickel

A similar hydrogenation of nitrolactam nitrile (LVIII) furnished a product, m.p.267-269° (LX).



(LVIII)



(LX)

Characterization of the compound, m.p.267-269° as 4-aza-A-homo--5-cyano-6α-amino-5α-cholestan-3-one (LX)

The compound, m.p.267-269° analysing for $C_{28}H_{47}N_3O$ suggested the formation of amine (LX). IR spectrum of this product exhibited absorption bands at 3520, 3360, 3210, 2240 and 1650 cm^{-1} which corresponds to NH_2, NHCO, C≡N and C=O functional groups. PMR spectrum showed a multiplet centred at δ 3.30 integrating for 5 protons could be assigned to C4a-2H, C2-2H and C6-βH. A broad signal for one proton at δ 7.00, exchangeable with D_2O, was due to NHCO proton. Another multiplet at δ 2.00 was found to be exchangeable with D_2O and thus assigned to NH_2 protons. Methyl protons were observed at δ 1.03, 0.93, 0.83 and 0.65.

Experimental

All the melting points (in ^{o}C) are uncorrected. IR spectra were measured with Pye-Unicam SP3-100 spectrophotometer and mass spectra on JMS-300 mass spectrometer. NMR spectra were run in $CDCl_3$ on a Varian A-60 instrument with TMS as the internal standard and chemical shifts expressed in ppm (δ). TLC were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid.

3β-Acetoxycholest-5-ene

A mixture of cholesterol (100 g), purified pyridine (150 ml) and freshly distilled acetic anhydride (100 ml) was heated on a steam bath for 2 hours. The resulting light brown solution was poured into crushed ice-water mixture with stirring. A light brown precipitate, thus obtained, was filtered under suction, washed with water (until free from pyridine) and dried in air. The crude product on crystallization from acetone gave the pure acetate. Yield, 90 g; m.p.114-115^{o} (reported[30] m.p.116^{o}).

3β-Acetoxy-6-nitrocholest-5-ene (XLVII)

3β-Acetoxycholest-5-ene (10 g) covered with nitric acid (d, 1.52; 250 ml) and sodium nitrite (5 g) was gradually added over a period of 1 hour with continuous stirring and keeping the temperature below 20^{o}. The stirring was further continued for

additional 2 hours, when a yellow spongy mass separated on the surface of the mixture. The whole mass extracted with ether, the ethereal layer was washed with water, then with sodium bicarbonate solution (5%) and finally with water. Removal of the solvent provided the nitro compound as an oil which was crystallized from methanol. Yield 6.5 g; m.p.103° (reported[31] m.p.102-104°).

3β-Hydroxy-6-nitrocholest-5-ene (XLVI)

A mixture of 3β-acetoxy-6-nitrocholest-5-ene (XLVII) (5.0 g), methanol (100 ml) and perchloric acid (60 ml) was refluxed on a steam bath for 2 hours. The solvent was then removed and the residue thus obtained was extracted with chloroform. The organic layer was washed successively with water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent and crystallization from methanol afforded nitro compound (XLVI). Yield, 4.2 g; m.p.129° (reported[32] m.p.129-131°).

Reaction of 3β-hydroxy-6-nitrocholest-5-ene (XLVI) with KCN: 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L)

A solution of nitro compound (XLVI) (5.0 g) in methanol-ether mixture (100 ml, 3:5) was poured over excess KCN. After a period of ~24 hours the reaction was over (progress of the

reaction was monitored through TLC). At the completion of reaction, the reaction mixture was poured over a large excess of water, and the solution extracted with ether, ethereal layer washed successively with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent on a steam bath followed by crystallization from methanol provided crystalline product (L). Yield, 4.0; m.p.140°.

IR(KBr) : ν_{max} 3420 (br, OH), 2250 (C≡N), 1560 and 1370 cm^{-1} (NO_2).

PMR($CDCl_3$) : δ 4.55 (m, 1H, W1/2=17 Hz, C6-β<u>H</u>), 3.97 (m, 1H, W1/2=18 Hz, C3-α<u>H</u>), 3.20 (br,s, 1H, exchangeable with D_2O, C3-O<u>H</u>), 1.07 (s, 3H, C10-C<u>H_3</u>), 0.67 (s, 3H, C13-C<u>H_3</u>), 0.92 and 0.82 (remaining methyl protons).

Analysis Found : C, 73.43; H, 10.09; N, 6.05,

$C_{28}H_{46}N_2O_3$ requires : C, 73.36; H, 10.04; N, 6.11%.

<u>Hydrogenation of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L) with H_2/Raney-nickel: 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (LIV)</u>

A mixture of compound (L) (1.0 g), methanol (50 ml) and freshly prepared Raney-nickel (ca 5.0 g) was taken in a hydrogenation flask. The reaction mixture was hydrogenated at hydrogen pressure of 30 psi, for a period of 2 hours, when the reaction completed (the reaction was performed at hydrogen pressure varying

from 20 to 50 psi, but the product obtained was invariably the same). At the completion of reaction, Raney-nickel was filtered off, the solvent evaporated to get an oily residue which was extracted with chloroform and the organic layer washed with water. Removal of the solvent and crystallization from methanol afforded (LIV). Yield, 0.85 g; m.p.185°.

IR(KBr) : ν_{max} 3410 (OH), 3350, 3300 (NH_2), 2235 (C≡N), 1620 and 900 cm^{-1} (NH-bending).

PMR($CDCl_3$): δ 4.00 (m, 1H, W1/2=19 Hz, C3-α$\underline{H}$), 3.40 (br,m, 1H, exchangeable with D_2O, C3-O$\underline{H}$), 2.80 (m, 1H, W1/2=24 Hz, C6-β$\underline{H}$), NH_2 protons merged with methylene protons (An area of two protons was found to be exchangeable with D_2O at 2.03), 0.95 (s, 3H, C10-C$\underline{H}_3$), 0.65 (s, 3H, C13-C$\underline{H}_3$), 0.90 and 0.81 other remaining methyl protons.

Analysis Found : C, 78.48; H, 11.25; N, 6.50,

$C_{28}H_{48}N_2O$ requires : C, 78.50; H, 11.21; N, 6.54%.

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVII) with KCN: 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI)

A solution of nitro compound (XLVII) (5.0 g) in methanol ether mixture (100 ml; 3:2) was poured over KCN (5.0 g). The reaction completed within 24 hours. After the completion of the

reaction, the reaction mixture was worked up in a similar way. Removal of the solvent gave an oily residue which was chromatographed over the silica gel column (80 g; BDH Bombay). Elution with petroleum-ether (15:1) afforded the product (LI). Yield, 2.1 g; m.p.213°.

IR(KBr) : ν_{max} 2245 (C≡N), 1740 (O-C(=O)-CH_3), 1565, 1370 (NO_2), 1248 and 1040 cm^{-1} (C-O).

PMR($CDCl_3$): δ 5.30 (m, 1H, W1/2=19 Hz, C3-α$\underline{H}$), 4.73 (m, 1H, W1/2=19 Hz, C6-β$\underline{H}$), 2.01 (s, 3H, C3-OC(=O)-$C\underline{H}_3$), 1.10 (s, 3H, C10-$C\underline{H}_3$), 0.70 (s, 3H, C13-$C\underline{H}_3$), 0.95 and 0.85 (remaining methyl protons).

Analysis Found : C, 72.09; H, 9.56; N, 5.65,

$C_{30}H_{48}N_2O_4$ requires : C, 72.00; H, 9.60; N, 5.60%.

Continued elution with petroleum-ether (10:1) provided a compound, m.p.140°; yield, 2.50 g. Moreover, this product was found identical with the compound (L) obtained by the reaction of (XLIV) with potassium cyanide.

The product (L) (1.0 g) was acetylated to get 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane with pyridine-acetic anhydride (20 ml; 1:1) by heating the reaction mixture on a steam bath under anhydrous condition. Yield 0.7 g.

Hydrogenation of 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI) with H_2/Raney-nickel: 3β-hydroxy-5-cyano-6α-amino-5α-cholestane (LIV)

Hydrogenation of product (LI) in a similar way furnished the only product (LIV) which melted at 185° and was found identical with the authentic sample (LIV) in all respects (m.p., m.m.p., co-TLC and IR).

3β-Chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100 g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated and kept at a temperature 50-60° on a water bath for 1 hour and then poured into cold water with stirring. The yellow solid thus obtained was filtered under suction and washed several times with water and air-dried. Crystallization from acetone gave 3β-chlorocholest-5-ene. Yield, 95.0 g; m.p.95-96° (reported[33] m.p.96-97°).

Cholest-5-ene

3β-Chlorocholest-5-ene (10 g) was dissolved in warm amyl alcohol (230 ml) and sodium metal (20 g) was added to the

solution with continuous stirring over a period of 8 hours. The reaction mixture was warmed occasionally when all the sodium metal dissolved, the reaction mixture was poured into water, acidified with hydrochloric acid (50%, 1.5 litres) and then allowed to stand over night. A white crystalline solid thus obtained was filtered under suction and washed thoroughly with water and air-dried. The crude material was recrystallized from acetone to provide cholest-5-ene as cubes. Yield, 8.5 g; m.p.94^{o} (reported[31] m.p.95^{o}).

6-Nitrocholest-5-ene (XLVIII)

A suspension of finely powdered cholest-5-ene (6.0 g) in glacial acetic acid (50 ml) was vigorously stirred below 20^{o} and treated with nitric acid (15 ml; d, 1.5) followed by the addition of sodium nitrite (3.0 g) over a period of 1 hour. The reaction mixture was poured into cold water after 4 hours stirring and the yellow product thus obtained was extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent provided the desired compound as an oil which was crystallized from ethanol as leaflets. Yield, 4.5 g; m.p.119-120^{o} (reported[34] m.p.120-121^{o}).

Reaction of 6-nitrocholest-5-ene (XLVIII) with KCN: 5-cyano-6α-nitro-5α-cholestane (LII)

The reaction procedure consists of the pouring of substrate (5.0 g) dissolved in methanol-ether mixture (200 ml; 3:2) over KCN (5.0 g) and keeping of the reaction mixture at room temperature for 24 hours. After the completion of the reaction, the reaction mixture worked up in a similar way. Removal of the solvent and subsequent crystallization from methanol gave the corresponding cyano compound (LII). Yield, 4.2 g; m.p.160° (reported[63] m.p.161°).

IR(KBr) : ν_{max} 2245 (C≡N), 1560 and 1390 cm^{-1} (NO_2).

PMR(CCl_4) : δ 4.50 (m, 1H, W1/2=16 Hz, C6-β<u>H</u>, 1.00 (s, 3H, C10-C<u>H</u>$_3$), 0.65 (s, 3H, C13-C<u>H</u>$_3$), 0.95 and 0.85 (remaining methyl protons).

Hydrogenation of 5-cyano-6α-nitro-5α-cholestane (LII) with H_2/Raney-nickel: 5-cyano-6α-amino-5α-cholestane (LV)

A mixture of compound (LII) (1.0 g), methanol (50 ml) and freshly prepared Raney-nickel (ca 5.0 g) was taken in a hydrogenation flask. The reaction mixture was hydrogenated at a hydrogen pressure of 30 psi, for a period of 2 hours, when the reaction completed(TLC). At the completion of reaction, Raney-

nickel was filtered off, the solvent evaporated to get an oily residue which was extracted with chloroform and the organic layer washed with water. Removal of the solvent and crystallization from methanol afforded (LV). Yield, 0.75; m.p.120°.

IR(KBr) : ν_{max} 3395, 3350 (NH_2), 2240 ($C\equiv N$), 1620 and 880 cm^{-1} (NH-bending).

PMR($CDCl_3$): δ 2.75 (m, 1H, W1/2=22 Hz, C6-β$\underline{H}$), NH_2 protons merged with methylene protons (exchangeable with D_2O), 0.95 (s, 3H, C10-$C\underline{H}_3$), 0.68 (s, 3H, C13-$C\underline{H}_3$), 0.93 and 0.83 (remaining methyl protons).

Analysis Found : C, 81.62; H, 11.50; N, 6.73;

$C_{28}H_{48}N_2$ requires : C, 81.55; H, 11.65; N, 6.79%.

3β-Chloro-6-nitrocholest-5-ene (XLIX)

To a well stirred mixture of 3β-chlorocholest-5-ene (12 g), glacial acetic acid (80 ml) and nitric acid (25 ml; d, 1.52) at a temperature below 20° was added sodium nitrite (6 g) gradually over a period of one and half hour. After the complete addition of sodium nitrite, the mixture was further stirred for about 2 hours. Ice cold water was then added to it and the yellowish solid thus separated, was filtered and air-dried. The desired product was crystallized from methanol as needles. Yield, 8.3 g; m.p.152° (reported[35] m.p.153°).

Reaction of 3β-chloro-6-nitrocholest-5-ene (XLIX) with KCN: 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII)

A solution of compound (XLIX) (5.0 g) in methanol-ether mixture (100 ml, 3:5) was poured over dry and powdered KCN (5.0 g). After a period of 24 hours, the reaction was over. At the completion of reaction, the reaction mixture was poured over a large excess of water and the solution extracted with ether. The ethereal layer washed successively with water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. The solvent was then evaporated on a steam bath and crystallized from methanol. Yield, 4.0 g; m.p.143°.

IR(KBr) : ν_{max} 2240 (C≡N), 1560, 1380 (NO_2), 780 cm^{-1} (C-Cl).

PMR($CDCl_3$): δ 4.50 (m, 1H, W1/2=18 Hz, C6-β<u>H</u>), 4.20 (m, 1H, W1/2=18 Hz, C3-α<u>H</u>), both signal partially overlapping, 1.10 (s, 3H, C10-C<u>H</u>$_3$), 0.67 (s, 3H, C13-C<u>H</u>$_3$), 0.90 and 0.75 (remaining methyl protons).

Analysis Found : C, 76.02; H, 10.40; N, 6.33;

$C_{28}H_{45}N_2O_2Cl$ requires C, 75.98; H, 10.45; N, 6.25%.

Hyerogenation of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII) with H_2/Raney-nickel 5-cyano-6α-amino-5α-cholestane (LV)

The hydrogenation of substrate (LIII) (1.0 g) with H_2/R-Ni in the similar way gave a product m.p.120° (0.5 g) which showed a negative Beilstein test and was found identical with the product (LV) in all respects.

Jone's oxidation of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L): 5-cyano-6α-nitro-5α-cholestan-3-one (LVI)

Compound (L) (1.0 g) in acetone (10 ml) was treated with Jone's reagent (2.0 ml) at 0-5° with shaking. After 1 hour, the reaction mixture poured into water and extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent and crystallization from methanol afforded (LVI). Yield, 0.70 g; m.p.155°.

IR(KBr) : ν_{max} 2245 (C≡N), 1715 (C=O), 1565, 1375 cm^{-1} (NO_2).

PMR($CDCl_3$): δ 4.75 (m, 1H, W1/2=20 Hz, C6-β<u>H</u>), 1.20 (s, 3H, C10-C<u>H</u>$_3$), 0.70 (s, 3H, C13-C<u>H</u>$_3$), 0.98 and 0.92 (remaining methyl protons).

Analysis Found : C, 73.61; H, 9.60; N, 6.08;

$C_{28}H_{44}N_2O_3$ requires : C, 73.68; H, 9.65; N, 6.14%.

Preparation of Jone's reagent

Chromium trioxide (35 g) was dissolved in water (100 ml). This solution was then maintained at 0°C. Concentrated sulphuric acid (35 ml) was added dropwise to the above solution during 30 minutes with occasional shaking. The solution (Jone's Reagent) thus prepared was kept in refrigerator for use.

Reaction of 5-cyano-6α-nitro-5α-cholestan-3-one (LVI) with hydrazoic acid: 3-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-4-one (LVII) and 4-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-3-one (LVIII)

A solution of hydrazoic acid (35 ml), was mixed with freshly distilled boron trifluoride etherate (2 ml) and to this was added a solution of (LVI) (3 g) in benzene (30 ml). Progress of the reaction was monitored by TLC. After the reaction was over (6 hours), benzene was removed under reduced pressure and the crude solid so obtained was chromatographed over a silica gel column. Elution with benzene-chloroform (25:1) gave the product (LVII) which was crystallized from methanol. Yield, 0.85 g; m.p.265°.

IR(KBr) : ν_{max} 3680-3375 (NH), 2240 (C≡N), 1675, 1660 (C=O), 1560 and 1390 cm^{-1} (NO_2).

PMR($CDCl_3$): ∂ 6.80 (br,s, 1H, exchangeable with D_2O, N<u>H</u>), 4.73 (m, W1/2=19 Hz, 1H, C6-β<u>H</u>), 3.30 (m, 2H, C2-<u>H_2</u>), 1.03 (s, 3H, C10-C<u>H_3</u>), 0.70 (s, 3H, C13-C<u>H_3</u>), 0.90 and 0.80 (remaining methyl protons).

Analysis Found : C, 71.40; H, 9.55; N, 8.98,

$C_{28}H_{45}N_3O_3$ requires : C, 71.34; H, 9.37; N, 8.92%.

Elution with benzene-chloroform (18:1) afforded the product (LVIII) which was crystallized from methanol. Yield, 0.92 g; m.p.260°.

IR(KBr) : ν_{max} 3550-3260 (br, NH), 2240 (C≡N), 1670, 1650 (C=O), 1550, 1375 cm^{-1} (NO_2).

PMR($CDCl_3$): ∂ 7.00 (br,m, 1H, exchangeable with D_2O, N<u>H</u>), 4.80 (m, W1/2=17 Hz, 1H, C6-β<u>H</u>), 3.40 (d-like, 2H, simplified to doublet upon D_2O shake, J=15 Hz, C4a-2H), 1.1 (s, 3H, C10-C<u>H_3</u>), 0.65 (s, 3H, C13-C<u>H_3</u>), 0.90 and 0.77 (remaining methyl protons).

Analysis Found : C, 71.38; H, 9.60; N, 8.95,

$C_{28}H_{45}N_3O_3$ requires : C, 71.34; H, 9.57; N, 8.92%.

Preparation of hydrazoic acid

Hydrazoic acid solution was prepared according to the method described by Moural and Syhora[36]. Sodium azide (8 g) was

dissolved in water (100 ml) and to this was added benzene (60 ml) at 0^{o}. Sulphuric acid (8 ml) at 0^{o} was added dropwise with continuous shaking of the solution over a period of 30 minutes. The organic layer was then separated in a separating funnel, dried over anhydrous sodium sulphate and filtered. This solution of hydrazoic acid was made upto 100 ml by adding benzene and used in the reaction with ketones.

Hydrogenation of 3-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-4-one (LVII) with H_2/Raney-nickel: 3-aza-A-homo-5-cyano-6α-amino-5α-cholestan-4-one (LIX)

A mixture of compound (LVII) (1.0 g) and freshly prepared Raney-nickel (ca 5.0 g) was taken in a hydrogenation flask and the mixture was put to reduction at 30 psi of hydrogen pressure. The reaction completed in 2 hours. The suspension was then filtered, filtrate removed under reduced pressure, and the solid material crystallized from methanol to obtain (LIX). Yield, 0.8 g; m.p.287-290^{o}.

IR(KBr) : ν_{max} 3600, 3320, 3290 (NH-CO, NH_2), 2240 (C≡N), 1670 (CO-NH), 1650, 900 cm^{-1} (NH-bending).

PMR($CDCl_3$+ DMSO-d_6): δ 6.60 (m, 1H, exchangeable with D_2O, CO-NH), 3.60 (m, 2H, C2-H_2), 2.5 (m, 3H, C4a-2H and C6-βH), 2.20

(m, 2H, exchangeable with D_2O, $N\underline{H}_2$), 1.04 (s, 3H, C10-$C\underline{H}_3$), 0.67 (s, 3H, C13-$C\underline{H}_3$), 0.95, 0.83 (remaining methyl protons).

Analysis Found : C, 76.25; H, 10.65; N, 9.52,

$C_{28}H_{47}N_3O$ requires : C, 76.20; H, 10.66; N, 9.50%.

Hydrogenation of 4-aza-A-homo-5-cyano-6α-nitro-5α-cholestan-3-one (LVIII) with H_2/Raney-nickel: 4-aza-A-homo-5-cyano-6α-amino-5α-cholestan-3-one (LX)

A similar hydrogenation of nitrolactam nitrile (LVIII) (1.0 g) furnished the corresponding amine (LX), which was crystallized from methanol. Yield, 0.75 g; m.p.267-269°.

IR(KBr) : ν_{max} 3520, 3360, 3210 (CO-$\underline{NH}$, $N\underline{H}_2$), 2240 (C N), 1675, 1655 ($\underline{CO}$-NH), 1650 and 880 cm^{-1} (NH-bending).

PMR($CDCl_3$+DMSO-d_6): δ 7.00 (m, 1H, exchangeable with D_2O, $\underline{NH}$-CO), 3.30 (m, 5H, C4a-$\underline{H}_2$, C2-2H and C6-β$\underline{H}$), 2.00 (m, 2H, exchangeable with D_2O, $N\underline{H}_2$), 1.03 (s, 3H, C10-CH_3), 0.65 (s, 3H, C13-$C\underline{H}_3$), 0.93 and 0.80 (remaining methyl protons).

Analysis Found : C, 76.28; H, 10.60; N, 9.48,

$C_{28}H_{47}N_3O$ requires : C, 76.20; H, 10.66; N, 9.50%.

Part Two

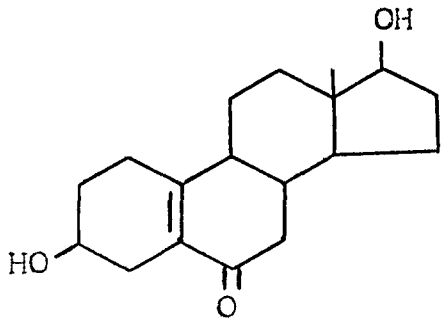
Steroidal Cyanoketones

Theoretical

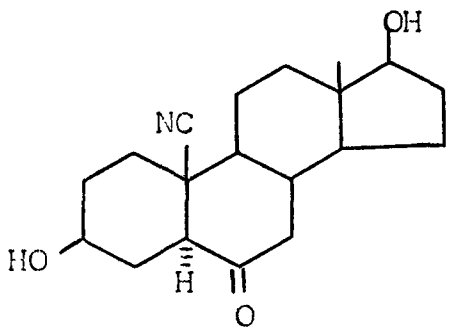
Cyanosteroids constitute a new class of biologically important compounds and demonstrate that the cyano group can be an important potentiating group for activity in steroids[37-41]. The preparation of cyanosteroids can be related to two types of reactions: Addition of hydrocyanic acid to unsaturated system and substitution of a suitable leaving group by cyanide ion[42]. But the introduction of cyanide group into the steroid nucleus has been reported by several workers mainly by the addition of hydrogen-cyanide using different methods.

The addition of hydrogen cyanide to carbon-carbon double bond is difficult and not proceeds satisfactorily, but it is favoured by electron withdrawing substituent at the olefinic double bonds. Consequently a wide variety of steroidal α,β-unsaturated ketones, aldehydes[43], carboxylic acid derivatives[44] and nitro compounds[45] etc. undergo addition of hydrogen cyanide in the presence of basic catalysts. The reaction conditions facilitate sometimes partial hydrolysis of the products, but hindered nitrile groups in angular position are not generally hydrolysed[46,47]. The synthesis of some typical steroidal cyano compounds and particularly cyano ketones are described in the following pages.

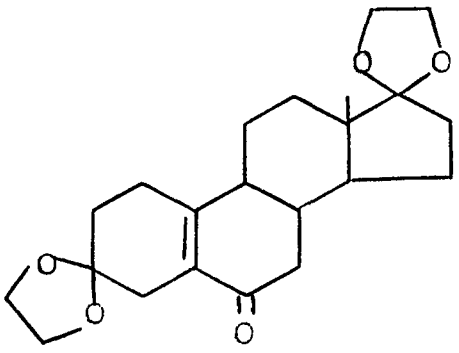
Fishman and Guzik[48] treated 3β,17β-dihydroxy estr-5(10)-en-6-one (LXI) with potassium cyanide in boiling ethylene to afford β-cyanoketone (LXIII). They repeated the same reaction on 3,17-bisdioxalene derivative (LXII) which gave product (LXIV) in high yield.



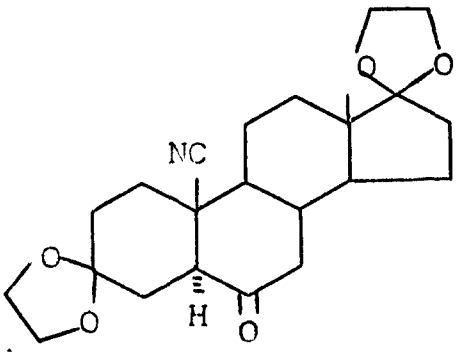
(LXI)



(LXIII)

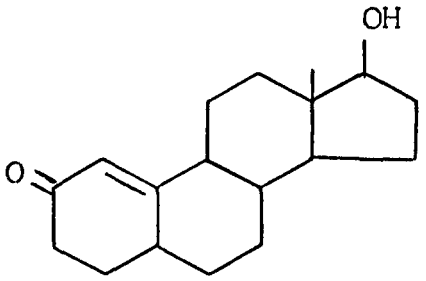


(LXII)

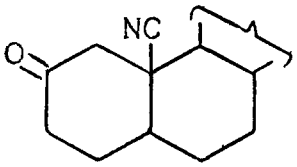


(LXIV)

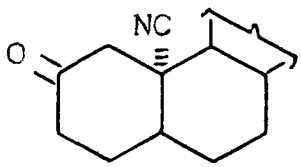
The reaction of 17β-hydroxy (LXV) with KCN in the presence of ammonium chloride proceeded smoothly to yield two isomeric cyanoketones (LXVI and LXVII)[49], which were separated by fractional crystallization.



(LXV)

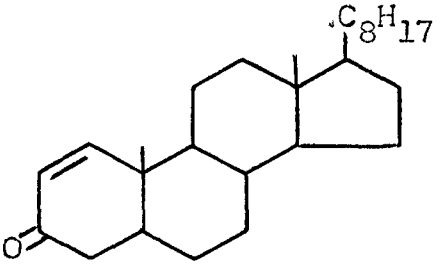


(LXVI)

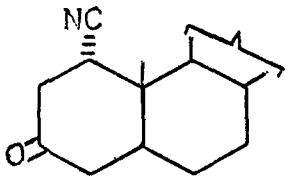


(LXVII)

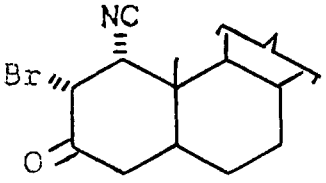
Glen and McLean[50] prepared 1α-cyano-5α-cholestan-3-one (LXIX) from 5α-cholest-1-en-3-one (LXVIII) using KCN and NH_4Cl. Derivative 2α-bromoketone (LXX) on dehydrobromination with LiCl furnished unsaturated cyanoketone (LXXI) while lactam (LXXII) was obtained by the hydrolysis of cyanoketone (LXIX) with potassium hydroxide.



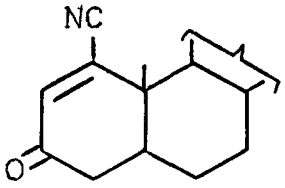
(LXVIII)



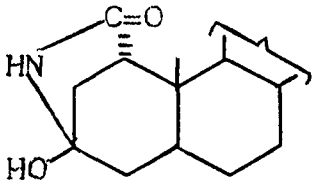
(LXIX)



(LXX)

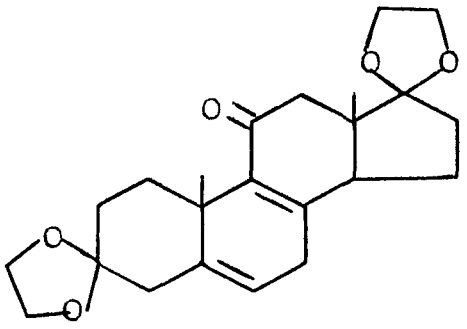


(LXXI)

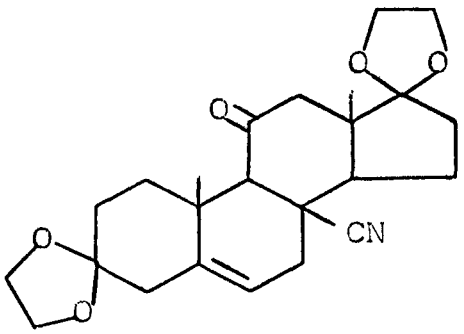


(LXXII)

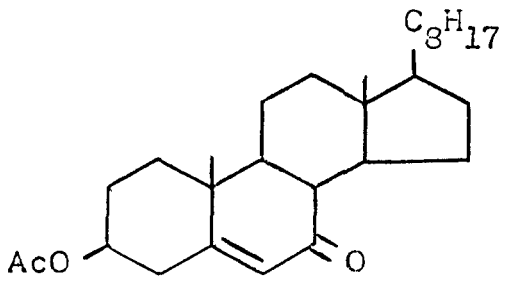
Nagata et al.[51-57] reported a new mode of hydrocyanation using hydrogen cyanide and an alkyl aluminium in aprotic solvents with different steroidal α,β-unsaturated ketones. Various alkyl aluminium cyanide or combination of alkyl aluminium and HCN were found to be excellent hydrocyanating reagents with high efficiency and high stereoselectivity. For example the treatment of 3,3:17, 17-bisethylenedioxyandrosta-5,8-dien-11-one (LXXIII) with HCN-$AlEt_3$ afforded 3,3:,17,17-bisethylenedioxy-11-oxoandrost-5-ene-8-carbonitrile (LXXV)[53], and 3β-acetoxycholest-5-ene-7-one (LXXIV) under similar conditions gave cyanoketone (LXXVI) in good yields.



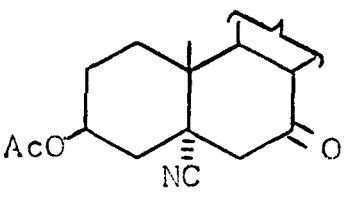
(LXXIII)



(LXXV)

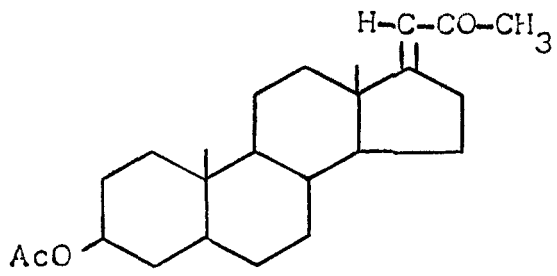


(LXXIV)

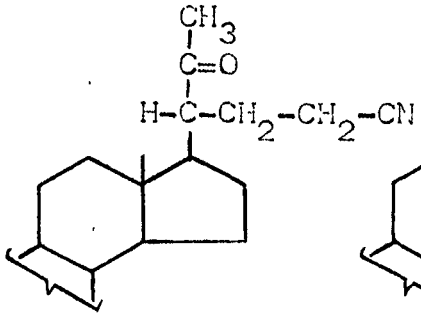


(LXXVI)

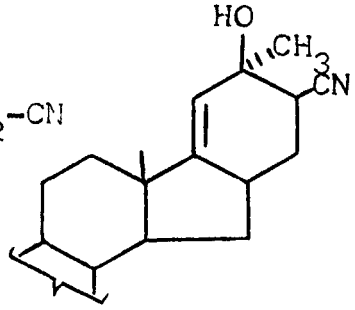
Engel et al.[58] carried out cyanoethylation of α,β-unsaturated ketones. The cyanoethylation of 3β-acetoxy-21-methyl-5α-pregn-17-ene-21-one (LXXVII) in benzene and sodium amylate as catalyst, gave a mixture of α-cyanoethylated ketone (LXXVIII) cyclized γ-cyanoethylation products (LXXIX and LXXX) and a dehydration product (LXXXI).



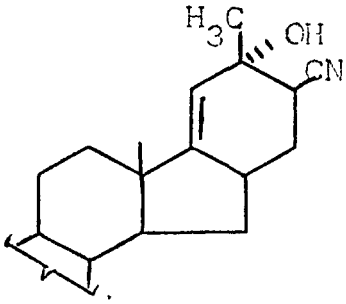
(LXXVII)



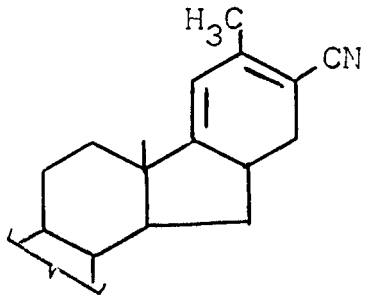
(LXXVIII)



(LXXIX)

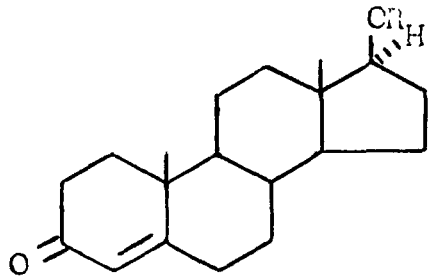


(LXXX)

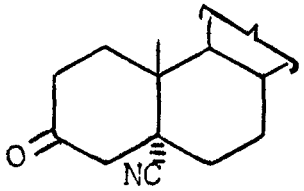


(LXXXI)

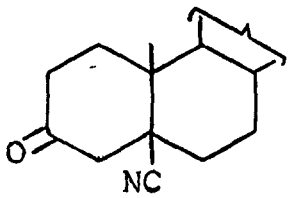
Bowers[59] reported the addition of hydrogen cyanide to testosterone and progesterone (LXXXII) which afforded complex reaction mixtures. Nitriles and amides epimeric at C5 were among the products obtained.



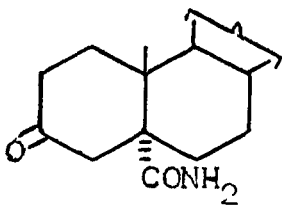
(LXXXII)



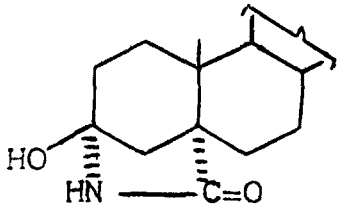
(LXXXIII)



(LXXXIV)

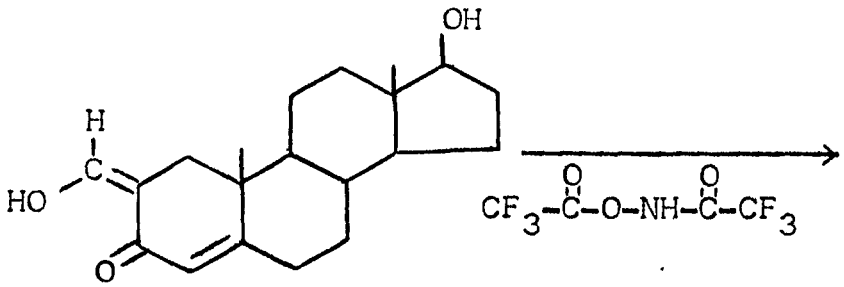


(LXXXV)

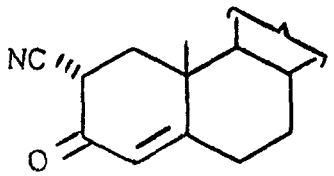


(LXXXVI)

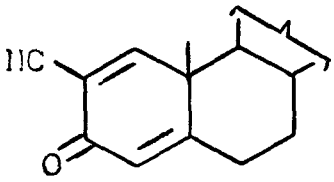
Kissman et al.[60,61] carried out the synthesis of α-cyanoketones. 2-Hydroxymethylene testosterone (LXXXVII) on treatment with two equivalents of trifluoroacetyl hydroxylamine in benzene furnished 2α-cyanotestosterone (LXXXVIII) in good yield. The reaction of (LXXXVIII) with 1,2-dichloro-5,6-dicyano-benzoquinone formed (LXXXIX)[62].



(LXXXVII)

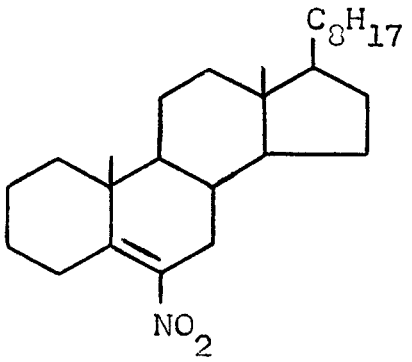


(LXXXVIII)

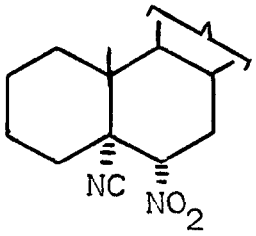


(LXXXIX)

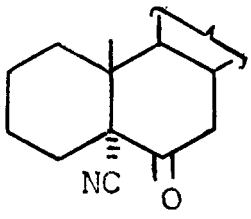
McKenna et al.[63] prepared 5α-cyano-6α-nitrocholestane (LII)[45] by refluxing 6-nitrocholest-5-ene (XLVIII) with KCN in methanol. 5α-Cyanocholestan-6-one (XC) and cholestan-4-en-6-one (XCI) were also isolated as side products from methanol residue.



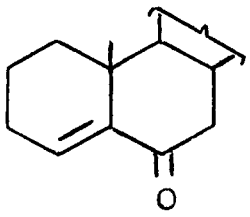
(XLVIII)



(LII)

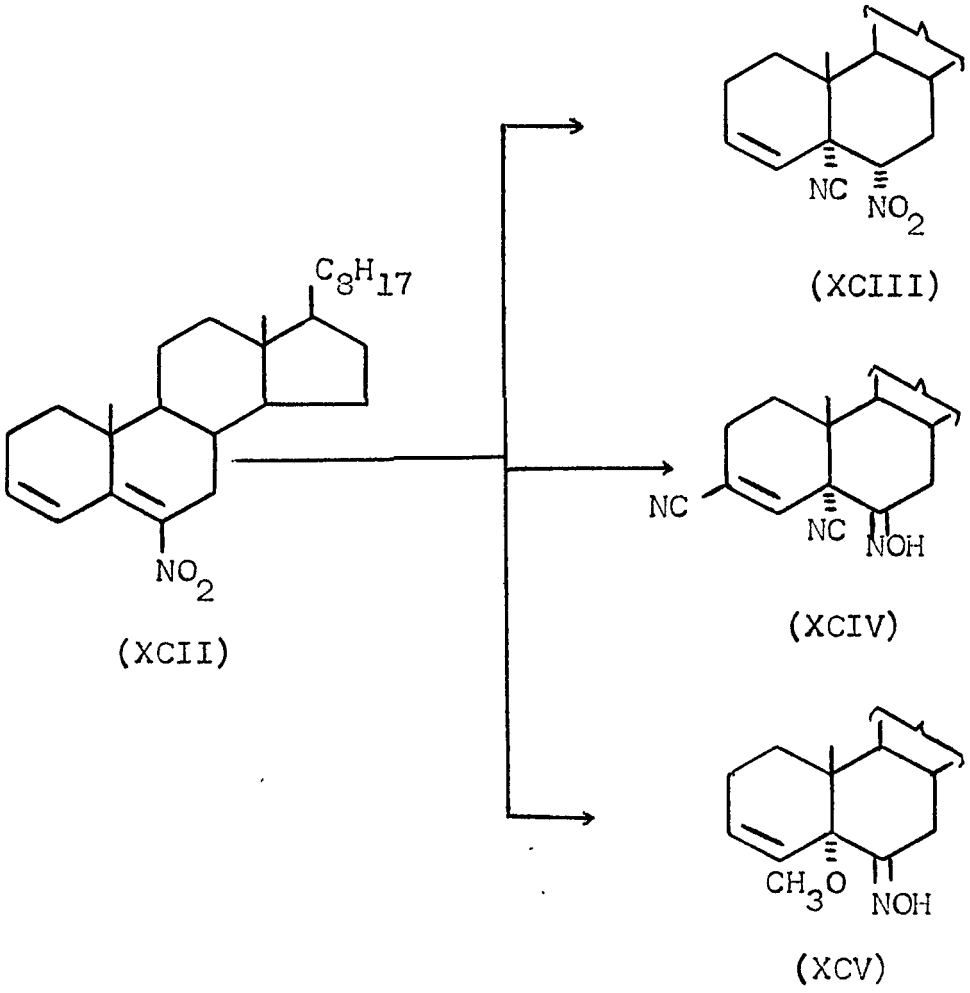


(XC)



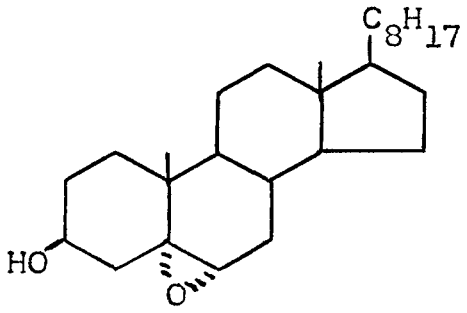
(XCI)

The addition of HCN to 6-nitrocholesta-3,5-diene (XCII) under basic conditions provided 5-cyano-6α-nitro-5α-cholest-3-ene (XCIII), 3,5-dicyano-6-oximino-5α-cholest-3-ene (XCIV) and its methoxy analogue (XCV). From these products were synthesised a number of related cyanosteroids[64].

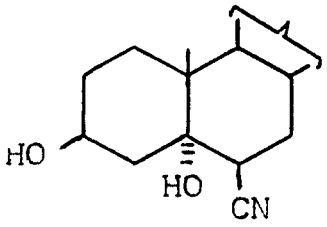


(XCII) (XCIII) (XCIV) (XCV)

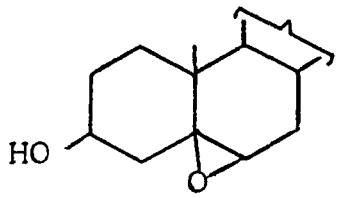
Nagata et al.[65] reported the addition of HCN on steroidal epoxides by using alkylaluminium and hydrogen cyanide in aprotic solvents, 3β-hydroxy-5,6α-oxido-5α-cholestane (XCVI) on treatment with HCN-$AlEt_3$ in THF afforded 3β,5-dihydroxy-6β-cyano-5α-cholestane (XCVIII) in almost quantitative yield. Similarly cholesterol 5,6β-epoxide (XCVII) was cleaved smoothly under similar conditons to 3β,6β-dihydroxy-5-cyano-5α-cholestane (XCIX).



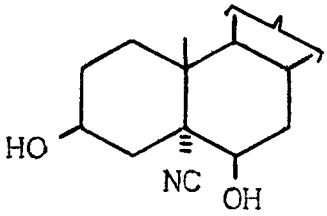
(XCVI)



(XCVIII)



(XCVII)

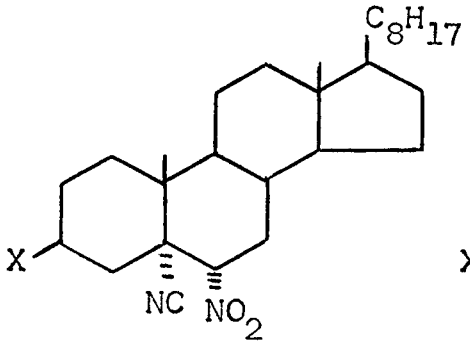


(XCIX)

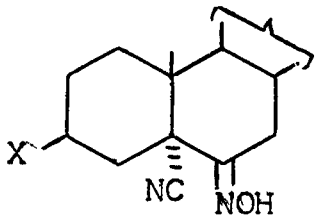
Discussion

In the recent past a number of papers describing the synthesis of β-cyanoketones through the Michael condensation of steroidal α,β-unsaturated ketones with KCN have been published. But the steroidal α-cyanoketones perhaps due to lack of a clear-cut procedure for their synthesis, were prepared to very little extent. 5-Cyano-5α-cholestan-6-ones (CIV-CVIII) and 6-oximino-5-cyano-5α-cholestanes (C-CIII) have been obtained through the Nef reaction of steroidal nitrocyanides (L-LIII). The oximes thus obtained in the reaction were further hydrolysed by refluxing the reaction mixture to respective 6-ones (CIV-CVIII) by a selective solvent system of hydrobromic acid and dioxane. Nef reaction[67,68] was achieved by pouring a solution of substrate (in sodium methoxide) into conc. sulphuric acid at 0-5°. The mixture was then mixed with ice cold water and extracted with ether to get a mixture of two products.

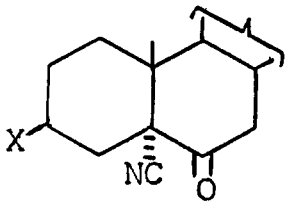
Our previous procedure for the preparation of oximes from steroidal nitroolefins[69] has also been successfully employed to convert steroidal nitrocyanides (L-LIII) into cyanooximes (C-CIII) in excellent yields using NH_3-Zn-MeOH as reagent.



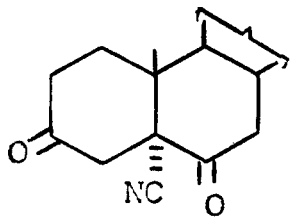
X	
(L)	-OH
(LI)	-OAc
(LII)	-H
(LIII)	-Cl



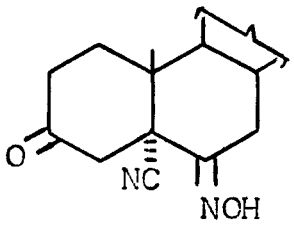
X	
(C)	-OH
(CI)	-OAc
(CII)	-H
(CIII)	-Cl



X	
(CIV)	-OH
(CV)	-OAc
(CVI)	-H
(CVII)	-Cl



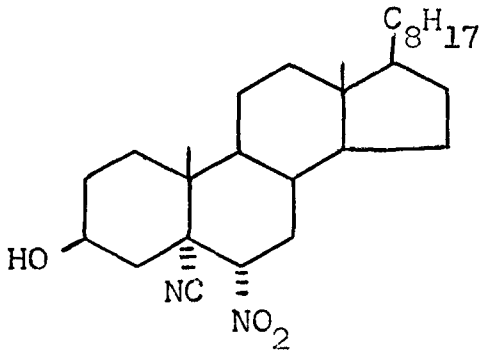
(CVIII)



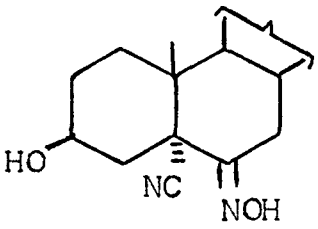
(CIX)

Nef reaction of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L)

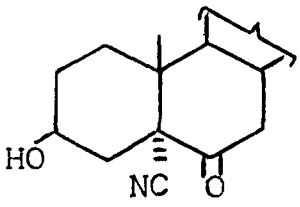
Nitrocyanide (L) when subjected to Nef reaction as described above, it yielded a mixture of two products, m.ps.215° and 105°.



(L)



(C)



(CIV)

Characterization of the compound, m.p.215°, as 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C)

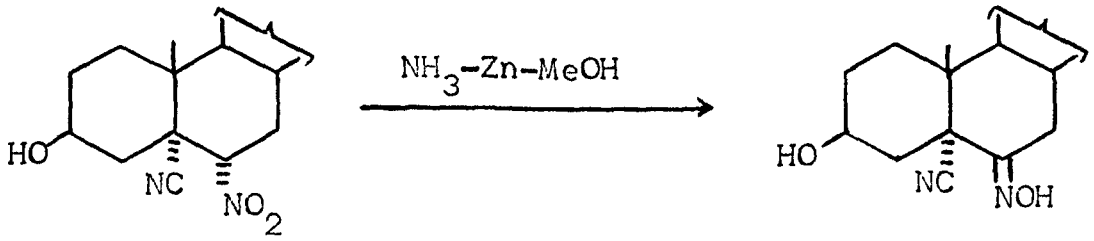
The compound, m.p.215° analysed for $C_{28}H_{46}N_2O_2$. The IR spectrum of this product showed absorption bands at 3500, 3320, 2240 and 1650 cm^{-1} which are due to the =NOH, OH, C≡N and C=N stretching frequencies respectively. PMR spectrum of this compound exhibiting singlet at δ 9.80 which is exchangeable with D_2O, is ascribable to oxime OH proton. A multiplet with (atδ 4.20) W1/2=20 Hz integrating for one proton is due to the C3-α proton. A broad signal at δ 3.85 for 1H (exchangeable with D_2O) can be assigned to the C3-O<u>H</u> proton. A doublet like signal with J=10 Hz at δ 3.35 for one proton is characteristic for the C7-proton of oximes. Methyl protons were observed at δ 0.90, 0.87, 0.82 and 0.67.

Characterization of the compound, m.p.105° as 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV)

The product, m.p.105° analysing for $C_{28}H_{45}NO_2$ gave its IR spectrum absorption bands at 3400, 2230 cm^{-1} which are compatible with OH, C≡N stretching frequencies, respectively. The appearance of a sharp strong band at 1725 cm^{-1} suggests the presence of ketone in the product. The hydrolysis of oxime (C) with HBr-dioxane giving the product (CIV) further supported the carbonyl function in the product (CIV) and oxime in compound (C).

Reaction of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L) with NH_3-Zn-MeOH

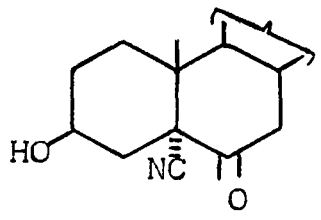
Nitrocyanide (L) dissolved in ether, was stirred with ammonia solution, methanol and zinc dust for half an hour at room temperature. The reaction mixture was worked up to obtain the product melting at 215° in good yield. This product was found to be identical with oxime (C) in all respects.



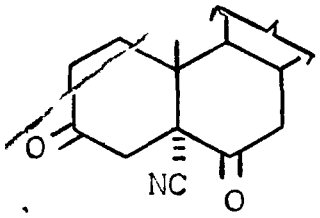
(L) (C)

Jone's oxidation of 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV)

The treatment of cyanoketone (CIV) with Jone's reagent at 0-5°, after usual work up and crystallization afforded a compound, m.p.191° (CVIII).



(CIV)



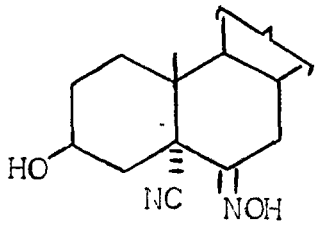
(CVIII)

Characterization of the compound m.p.191° as 5-cyano-5α-cholestane-3,6-dione (CVIII)

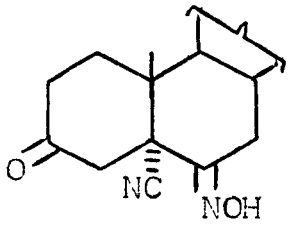
The compound m.p.191° was analysed for $C_{28}H_{43}NO_2$. Its IR spectrum showed bifurcated absorption band at 1710 and 1730 cm^{-1}. The latter band can be unambiguously assigned to the C6-carbonyl group while the former appearing at normal value corresponds to the C3-carbonyl function. An absorption band for cyano group was observed at 2230 cm^{-1}.

Jone's oxidation of 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C)

Cyanooxime (C) on treatment with Jone's reagent below 5°, after usual work up and crystallization gave a product, melting at 207°.



(C)



(CIX)

Characterization of the compound, m.p.207 as 5-cyano-6-oximino-5α-cholestan-3-one (CIX)

The compound, m.p.207° analysing for $C_{28}H_{44}N_2O_2$ showed absorption bands in its IR spectrum at 3480, 2230 and 1650 cm^{-1} which correspond to =NOH, C≡N and C=N respectively. A sharp band at 1710 cm^{-1} is assigned to C3-carbonyl group. PMR spectrum showed a singlet for one proton at δ 9.65 which is exchangeable with D_2O and ascribable to oxime-OH proton. A doublet with J=10 Hz at δ 3.40 is for one of the C7-proton. Methyl signals were seen at δ 0.92, 0.85, 0.70 and 0.65.

The hydrolysis of the ketooxime (CIX) with HBr-dioxane giving product (CVIII) further supported the characterization.

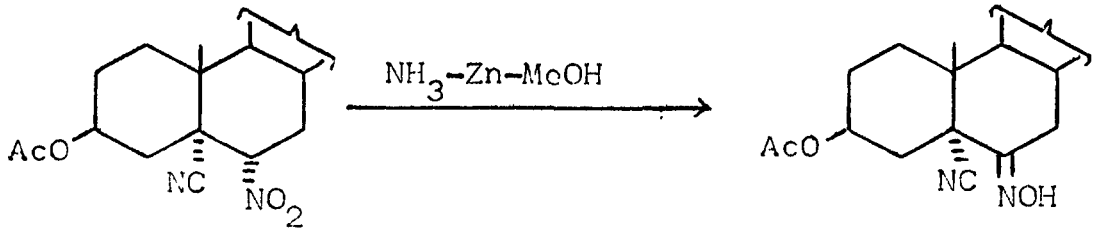
Nef reaction of 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI)

The treatment of nitrocyanide (LI) and sodium methoxide with conc. sulphuric acid gave a mixture of two products melting at 215 and 105° identical in all respects (m.p., m.m.p., co-TLC

and IR) with 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C) and 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV) respectively. Acetate group was hydrolysed due to the alkaline conditions of the reaction and thus the desired products (CI) and (CV) were not obtained.

Reaction of 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI) with NH_3-Zn-MeOH

The nitro compound (LI) in ether was stirred with ammonia solution, zinc dust and methanol and the reaction mixture was worked up to obtain the single product, m.p.221°.



(LI) (CI)

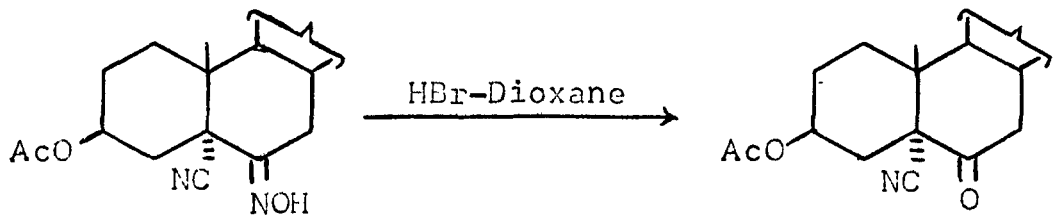
Characterization of the compound, m.p.221°, as 3β-acetoxy-5-cyano-6-oximino-5α-cholestane (CI)

The product m.p.221° was analysed for $C_{30}H_{48}N_2O_3$. IR spectrum of the compound showed a sharp band at 3460 cm^{-1} which is compatible with the stretching frequency of OH of oxime. Bands at 2230, 1730 and 1650 cm^{-1} correspond to the C≡N, acetate C=O

and C=N stretching frequencies respectively. Its PMR spectrum exhibiting a one proton sharp singlet at δ 8.50 (exchangeable with D_2O) is ascribable to oxime proton. A multiplet showing W1/2=20 Hz at δ 5.20 for one proton (C3-αH) suggested the trans A/B ring junction. A doublet J=11 Hz at δ 3.35 integrating for one proton is assignable to one of the C7-protons. A singlet for 3 protons at δ 2.05 is due to the acetate protons. Methyl protons were seen at δ 0.94 (C10-CH_3), 0.67 (C13-CH_3), 0.87 and 0.82 (remaining methyl protons).

Conversion of oxime (CI) to 3β-acetoxy-5-cyano-5α-cholestan-6-one (CV)

3β-Acetoxy-5-cyano-6-oximino-5α-cholestane (CI) was refluxed with hydrobromic acid in dioxane and the reaction mixture was worked up to yield the product (CV), m.p.122°.



(CI) (CV)

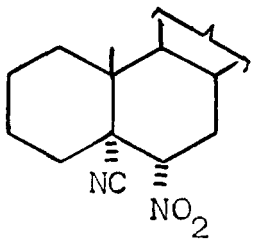
The compound m.p.122° showing elemental analysis for $C_{30}H_{47}NO_3$ and absorption bands at 2235 (C≡N), 1725 (C=O) and

1730 cm^{-1} for acetate C=O, confirmed the formation of 3β-acetoxy-5-cyano-5α-cholestan-6-one (CV).

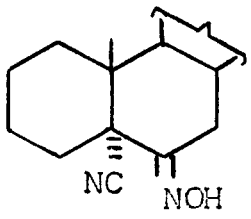
3β-Hydroxy-5-cyano-5α-cholestan-6-one (CIV) on treatment with acetic anhydride and pyridine transformed to cyanoketone (CV).

Nef Reaction of 5-cyano-6α-nitro-5α-cholestane (LII)

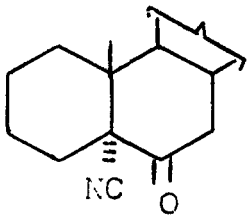
The treatment of nitrocyanide (LII) and sodium methoxide with conc. sulphuric acid under Nef reaction condition gave after usual work up of the reaction and column chromatography two products m.ps.178° (CII) and 119° (CVI).



(LII)



(CII)



(CVI)

Characterization of the compound, m.p.178°, as 5-cyano-6-oximino-5α-cholestane (CII)

The product melting at 178° analysed for $C_{28}H_{46}N_2O$ and showed absorption bands in its IR spectrum at 3400, 2240 and 1670 cm^{-1} which correspond to =NOH, C≡N and C=N stretching frequencies.

PMR spectrum supported its assignment as oxime (CII). It showed a singlet for one proton at δ 8.83 which is exchangeable with D_2O and ascribable to oxime -OH proton. A doublet with J=11 Hz at δ 3.36 could be assigned to one of the C7-protons adjacent to the C=N of oxime. Methyl protons were observed at δ 0.90, 0.86, 0.83 and 0.63.

Characterization of the compound, m.p.119° as 5-cyano-5α-cholestan-6-one (CVI)

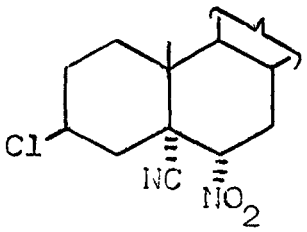
The compound, m.p.119° (Reported[63].m.p.120°) showed a characteristic band for carbonyl frequency at 1725 cm^{-1} in its IR spectrum. A sharp medium band at 2240 cm^{-1} was due to C≡N stretching frequency. Oxime (CII) when subjected to hydrolysis gave a product which was found to be identical with the ketone (CVI) in all respects.

Reaction of 5-cyano-6α-nitro-5α-cholestane (LII) with NH_3-Zn-MeOH

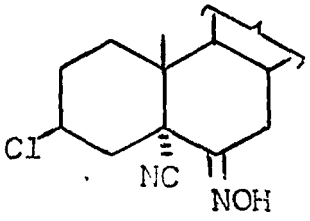
The reaction of nitrocyanide (LII) with the reagent NH_3-Zn-MeOH was performed in the usual manner. Subsequent work up and crystallization provided a compound, m.p.178°. This product was found to be 5-cyano-6-oximino-5α-cholestane (CII) by direct comparison with the authentic sample (m.p., m.m.p., co-TLC and IR).

Nef Reaction of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII)

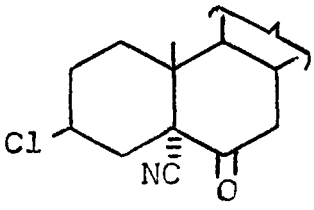
A similar treatment of nitrocyanide (LIII) under Nef condition afforded two products with m.ps.182° and 147°.



(LIII)



(CIII)



(CVII)

Characterization of the compound m.p.182° as 3β-chloro-5-cyano-6-oximino-5α-cholestane (CIII)

The compound, m.p.182° analysing for $C_{28}H_{45}N_2OCl$ showed absorption bands in its IR spectrum at 3500, 2240, 1660 cm^{-1} which correspond to =NOH, C≡N and C=N stretching frequencies respectively. PMR spectrum of this product showing a sharp one proton (NOH) singlet at δ 8.53 which is exchangeable with D_2O, supports the assignment as oxime. A multiplet with W1/2=22 Hz at δ 4.30 integrating for one proton is due to C3-αH. A doublet with J=10 Hz appearing at δ 3.40 for one of the C7-protons is characteristic of the oximes. Methyl signals were seen at δ 0.91, 0.88, 0.83 and 0.67.

Characterization of the compound m.p.147° as 3β-chloro-5-cyano-5α-cholestan-6-one (CVII)

The compound, m.p.147° analysing for $C_{28}H_{44}NOCl$ showed a characteristic band for the carbonyl function at 1730 cm^{-1}. Other bands at 2230 and 760 cm^{-1} were seen for the C≡N and C-Cl stretching frequencies respectively. Further evidence in favour of ketone came from the hydrolysis of oxime (CIII) which furnished a compound identical to ketone (CVII) in all respects.

Reaction of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII) with NH_3-Zn-MeOH

The compound (LIII) dissolved in ether, was treated with NH_3-Zn-MeOH as usual. Then the reaction mixture was extracted with ether and crystallized from methanol gave a single product, m.p.182° in good yield. This product was found to be identical with oxime (CIII) in all respects (m.p., m.m.p., co-TLC and IR).

The notable feature in the IR spectra of the cyanooximes is the appearance of comparatively sharp bands [very sharp in the case of oxime(CIII)] shifted slightly to longer wavelengths (3500-3400 cm^{-1}) in contrast to the broad absorption bands for the corresponding OH stretching in 6-oximino-5α-cholestanes[69]. This phenomenon can be explained by considering the intramolecular hydrogen bonding[70,71] between the oxime OH and CN groups in these

products. The hydrolysis of the cyanooximes to the ketones taking longer reaction period and higher temperature supports the above viewpoint.

Nef reaction mainly consists in the formation of aldehydes and ketones by the addition of sodium salts of primary or secondary nitro compounds to an excess of cold mineral acids. But the nitro cyanides (L-LIII) under Nef reaction conditions gave ketones and oximes together. The formation of these oximes can be explained by again considering the stability which prevented their smooth hydrolysis to ketones during the Nef reaction.

A noteworthy point regarding the IR spectra of the cyano-ketones[60,63] is a 15-20 cm^{-1} increase in the frequency of C6 carbonyl group in comparison to the normal frequency of this function in α-unsubstituted steroidal 6-ones. This is due to the presence of CN group α to the carbonyl group which shifts the C=O band to a higher frequency as has been observed in the case of α-haloketones[72]. This effect is quite evident in the IR spectrum of the cyanodiketone (CVIII) which exhibited a bifurcated band at 1710 and 1730 cm^{-1}. The latter band can be unambiguously assigned to the C6 carbonyl function while the former appearing at the normal value corresponds to the C3 carbonyl function.

Previously reported procedure[69] for the conversion of olefinic nitro compounds into the respective oximes was successfully

applied on saturated nitro compounds. This method with NH_3-Zn-MeOH reagent system appeared to be better method for the conversion of nitrocyanide (L-LIII) to oximes in good yields as compared to the Nef reaction where oximes and ketone formed together were separated on silica gel column in low yields.

Experimental

Nef reaction of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L): 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV) and 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C)

3β-Hydroxy-5-cyano-6α-nitro-5α-cholestane (L) (3.0 g) was dissolved in sodium methoxide (100 ml) prepared by the reaction of 5.0 g sodium in 100 ml absolute methanol and the solution was refluxed on water bath for one hour. This solution (at 0-5°) was then added dropwise to concentrated sulfuric acid (250 ml) maintained at 0-5° in an ice bath, over a period of 30 minutes. The reaction mixture was left for additional half an hour in the ice bath with occasional shaking. Then, crushed ice was added to it and the compound thus precipitated was washed successively with water, sodium bicarbonate solution (~ 5%), water and dried over anhydrous sodium sulphate and filtered. Removal of the solvent gave an oily residue which was chromatographed over a silica gel (40 g; BDH, Bombay) column. Elution with benzene-ethylacetate (30:1) provided pure 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV) which was crystallized from alcohol. Yield, 0.70 g; m.p.105°.

IR(KBr) : ν_{max} 3400 (broad, C3-OH), 2230 (C≡N) and 1725 cm^{-1} (C=O).

Analysis Found : C, 78.75; H, 10.50; N, 3.20,

$C_{28}H_{45}NO_2$ requires : C, 78.69; H, 10.54; N, 3.23%.

Further elution with benzene-ethyl acetate (15:1) yielded 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C), crystallized from methanol. Yield, 0.65 g; m.p.215°.

IR(KBr) : ν_{max} 3500 (sharp, =NOH), 3320 (broad, OH), 2240 (C≡N) and 1650 cm^{-1} (C=N).

PMR($CDCl_3$) : δ 9.80 (s, 1H, exchangeable with D_2O, =N-OH), 4.20 (m, W1/2=20 Hz, 1H, C3-αH), 3.85 (broad, 1H, exchangeable with D_2O, C3-OH), 3.35 (d-like, J=10 Hz, 1H, C7-H), 0.90 (s, 3H, C10-CH_3), 0.67 (s, 3H, C13-CH_3), 0.87 and 0.82 ppm (remaining methyl protons).

Analysis Found : C, 76.12; H, 10.54; N, 6.40,

$C_{28}H_{46}N_2O_2$ requires : C, 76.02; H, 10.42; N, 6.33%.

Reaction of 3β-hydroxy-5-cyano-6α-nitro-5α-cholestane (L) with NH_3-Zn-MeOH: 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C)

Nitrocyanide (L) (2 g) was dissolved in ether-methanol mixture (100 ml, 1:1). To this solution was added ammonia solution (sp. gr. 0.91; 40 ml) and zinc dust (8 g) at room temperature (25-35°) and the progress of the reaction monitored by TLC. The reaction was over within 20-30 minutes. Thereafter, the suspension filtered, the filtrate reduced on a steam bath, the residue mixed

with 500 ml water and extracted with ether. The ether layer was washed with water, dried over anhyd. Na_2SO_4 and the solvent evaporated to get a solid which on crystallization from methanol provided the oxime (C) yield 1.5 g; m.p.215°.

Conversion of 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C) into 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV)

A mixture of oxime (C) (1.0 g) in dioxane (20 ml) and hydrobromic acid (10 ml, 40%) was refluxed on a heating mantel for 24 hours by which time the reaction completed (TLC). Excess dioxane was then removed on reduced pressure and mixed with large amount of water. The compound thus precipitated was extracted with ether and ethereal layer washed repeatedly with water and dried over anhyd. sodium sulphate. Removal of the solvent gave an oily residue which was crystallized from alcohol. Yield, 0.75 g; m.p. and m.m.p.105°.

Jone's oxidation of 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV) 5-cyano-5α-cholestane-3,6-dione (CVIII)

The substrate(CIV)(1 g) was dissolved in acetone (50 ml) and the solution cooled to 0°. To this, was added Jone's reagent (10 ml) dropwise over a period of 15 minutes. The reaction mixture was continuously stirred. It was then mixed with ice cold water and extracted with ether. The ethereal layer was washed success-

ively with water, sodium bicarbonate solution (~ 5%) and water, the ether solution was then dried over anhyd. sodium sulphate and filtered. Removal of the solvent and subsequent crystallization from methanol gave 5-cyano-5α-cholestane-3,6-dione (CVIII). Yield, 0.70 g; m.p.191°.

IR(KBr) : ν_{max} 2230 (C≡N), 1730 (C6-CO) and 1710 cm^{-1} (C3-CO).

Analysis Found : C, 79.10; H, 10.20; N, 3.26,

$C_{28}H_{43}NO_2$ requires : C, 79.06; H, 10.12; N, 3.29%.

Jone's oxidation of 3β-hydroxy-5-cyano-6-oximino-5α-cholestane (C): 5-cyano-6-oximino-5α-cholestan-3-one (CIX)

The cyanooxime (C) (1.0 g) was dissolved in acetone (50 ml) and the solution cooled to 0°. To this was added Jone's reagent (10 ml) dropwise over a period of 15 minutes and extracted with ether in the usual manner. Removal of the solvent and subsequent crystallization from methanol gave 5-cyano-6-oximino-5α-cholestan-3-one (CIX). Yield, 0.85 g; m.p.207°.

IR(KBr) : ν_{max} 3480 (sharp, =N-OH), 2230 (C≡N), 1710 (C3-CO), 1650 cm^{-1} (C=N).

PMR($CDCl_3$+ $DMSO-d_6$) : δ 9.65 (s, 1H, exchangeable with D_2O, =N-O<u>H</u>), 3.40 (d, J=10 Hz, 1H, C7-<u>H</u>), 0.92 (s, 3H, C10-C<u>H</u>$_3$),

0.65 (s, 3H, C13-C$\underline{H}_3$), 0.85 and 0.70 (remaining methyl protons).

Analysis Found : C, 76.27; H, 9.89; N, 6.28,

$C_{28}H_{44}N_2O_2$ requires : C, 76.36; H, 10.00;N, 6.36%.

Reaction of 3β-acetoxy-5-cyano-6α-nitro-5α-cholestane (LI) with NH_3-Zn-MeOH: 3β-acetoxy-5-cyano-6-oximino-5α-cholestane (CI)

A solution of nitrocyanide (LI) (2 g) dissolved in ether (50 ml), methanol (50 ml) and liquor ammonia (sp. gr. 0.91, 30 ml) was stirred at room temperature and zinc dust (8 g) was added to it. After the completion of reaction (30 minutes), the reaction mixture filtered, mixed with water (500 ml) and extracted with ether and dried over anhyd. sodium sulphate. Removal of the solvent gave solid residue which was crystallized from methanol to give a crystalline product (CI). Yield, 0.80 g; m.p.221°.

IR(KBr) : ν_{max} 3460 (sharp, =NOH), 2230 (C≡N), 1730 (acetate C=O), 1650 (C=N), 1230 and 1040 cm^{-1} (acetate C-O).

PMR($CDCl_3$) : δ 8.50 (sharp, s, 1H, =N-O$\underline{H}$), 5.20 (m, W1/2=20 Hz, 1H, C3-α$\underline{H}$), 3.35 (d, J=11 Hz, 1H, C7-$\underline{H}$), 2.05 (s, 3H, OCOC$\underline{H}_3$), 0.94 (s, 3H, C10-C$\underline{H}_3$), 0.67 (s, 3H, C13-C$\underline{H}_3$), 0.87 and 0.82 (other methyl protons).

Analysis Found : C, 74.50; H, 10.00; N, 5.85,

$C_{30}H_{48}N_2O_3$ requires : C, 74.38; H, 9.92; N, 5.79%.

Hydrolysis of 3β-acetoxy-5-cyano-6-oximino-5α-cholestane (CI): 3β-acetoxy-5-cyano-5α-cholestan-6-one (CV)

To a solution of oxime (CI) (1 g) in dioxane (20 ml) was mixed with hydrobromic acid (10 ml, 40%) and the reaction mixture refluxed for 12 hours. After the completion of the reaction mixture was poured into water and extracted with ether as usual and dried over anhyd. sodium sulphate. Removal of the solvent and subsequent crystallization afforded the compound (CV). Yield, 0.85 g; m.p.122°.

IR(KBr) : ν_{max} 2235 (C≡N), 1725 (C6-CO), 1730 ($OCOCH_3$ merged together), 1230 and 1050 cm^{-1} (acetate C-O).

Analysis Found : C, 76.82; H, 10.10; N, 3.04,

$C_{30}H_{47}NO_3$ requires : C, 76.76; H, 10.02; N, 2.99%.

Acetylation of 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV): 3β-acetoxy-5-cyano-5α-cholestan-6-one (CV)

3β-Hydroxy-5-cyano-5α-cholestan-6-one (CIV) (1 g) was heated with acetic anhydride (10 ml) and freshly distilled pyridine (10 ml) on a water bath for 2 hours. The reaction

mixture was poured into water. The solid material thus precipitated was extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%), water and dried over anhyd. sodium sulphate. Removal of the solvent followed by crystallization from methanol gave the product (CV). Yield, 0.8 g; m.p.122°.

Nef reaction of 5-cyano-6α-nitro-5α-cholestane (LII): 5-cyano-5α-cholestan-6-one (CVI) and 5-cyano-6-oximino-5α-cholestane (CII)

A solution of nitrocyanide (LII) (2.0 g) in sodium methoxide (100 ml) was refluxed for one hour. It was then cooled to 0-5° and added dropwise to conc. sulphuric acid (250 ml) maintained at 0-5° in an ice bath, over a period of half an hour with shaking. After the completion of reaction (~2 hours), the reaction mixture was mixed with crushed ice and worked up with ether in the usual manner. The ethereal solution was then dried over anhydrous sodium sulphate and filtered. Removal of the solvent and column chromatography of the residue over a silica gel (60 g) column, on elution with petrol provided 5-cyano-5α-cholestan-6-one (CVI), which was crystallized from methanol. Yield, 0.60 g; m.p.119° (reported[63] m.p.120°).

IR(KBr) : ν_{max} 2240 (C≡N) and 1725 (C=O).

Further elution with petrol-ether (15:1) afforded 5-cyano-6-oximino-5α-cholestane (CII) (crystallized from methanol). Yield, 0.45 g; m.p.178°.

IR(KBr) : ν_{max} 3400 (sharp, =NOH), 2240 (C≡N) and 1670 cm^{-1} (C=N).

PMR($CDCl_3$) : δ 8.83 (s, 1H, exchangeable with D_2O, =NOH), 3.36 (d, J=11 Hz, 1H, C7-H), 0.90 (s, 3H, C10-CH_3), 0.63 (s, 3H, C13-CH_3), 0.86 and 0.83 (remaining methyl protons).

Analysis Found : C, 78.79; H, 10.91; N, 6.48,

$C_{28}H_{46}N_2O$ requires : C, 78.87; H, 10.80; N, 6.57%.

Reaction of 5-cyano-6α-nitro-5α-cholestane (LII) with NH_3-Zn-MeOH: 5-cyano-6-oximino-5α-cholestane (CII)

5-Cyano-6α-nitro-5α-cholestane (LII) (2 g) was dissolved in ether methanol mixture (100 ml, 1:1). To this solution was added liquor ammonia (40 ml) and zinc dust (8 g) at room temperature and the progress of the reaction monitored by TLC. The reaction was over within 30-40 minutes. Thereafter, the suspension filtered, the filtrate reduced on steam bath, the residue mixed with large amount of water and extracted with ether as usual. Removal of the solvent gave a solid residue which on crystallization from methanol provided the oxime (CII). Yield, 1.52 g;m.p.178°.

Hydrolysis of 5-cyano-6-oximino-5α-cholestane (CII): 5-cyano-5α-cholestan-6-one (CVI)

Oxime (CII) (1.0 g) taken in a flask containing dioxane (20 ml) and hydrobromic acid (40%, 10 ml), was refluxed on a heating mantel for 24 hours. Excess dioxane was removed under reduced pressure and the reaction mixture was mixed with a large amount of water. Usual work up of the reaction mixture and removal of the solvent gave an oily residue which was crystallized from methanol to obtain the ketone (CVI). Yield, 0.7 g; m.p.119°.

Nef reaction of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII): 3β-chloro-5-cyano-5α-cholestan-6-one (CVII) and 3β-chloro-5-cyano-6-oximino-5α-cholestane (CIII)

3β-Chloro-5-cyano-6α-nitro-5α-cholestane (LIII) (2.0 g) was dissolved in sodium methoxide (~100 ml) (5.0 g sodium reacted with 100 ml absolute methanol) and the solution refluxed on a water bath for one hour. The reaction mixture was then cooled (0-5°) and added dropwise to conc. sulphuric acid (250 ml) maintained at 0-5° in an ice bath over a period of half an hour with occasional shaking. It was left for additional half an hour in the ice bath. Then, crushed ice was added to it and the solid material thus precipitated was extracted with ether. The ethereal layer washed with water, sodium bicarbonate solution (5%) water and dried over

anhyd. sodium sulphate. The solution was then filtered and the solvent was removed on a steam-bath to get an oily residue which was chromatographed over a silica gel (60 g; BDH, Bombay) column. Elution with petrol gave 3β-chloro-5-cyano-5α-cholestan-6-one (CVII), which was crystallized from methanol. Yield, 0.65 g; m.p.147°.

IR(KBr) : ν_{max} 2230 (C≡N), 1730 (C=O) and 760 cm^{-1} (C-Cl).

Analysis Found : C, 75.49; H, 9.94; N, 3.20,

$C_{28}H_{44}NOCl$ requires : C, 75.42; H, 9.88; N, 3.14%.

Further elution with petrol-ether (20:1) afforded the oxime (CIII), crystallized from methanol. Yield, 0.50 g; m.p.182°.

IR(KBr) : ν_{max} 3500 (very sharp, =NOH), 2240 (C≡N) and 740 cm^{-1} (C-Cl).

PMR($CDCl_3$) : δ 8.53 (sharp s, 1H, exchangeable with D_2O, =NO<u>H</u>), 4.30 (m, W1/2=22 Hz, 1H, C3-α<u>H</u>), 3.40 (d, J=10 Hz, 1H, C7-<u>H</u>), 0.91 (s, 3H, C10-C<u>H</u>$_3$), 0.67 (s, C13-C<u>H</u>$_3$), 0.88 and 0.83 (remaining methyl protons).

Analysis Found : C, 72.88; H, 9.85; N, 6.00,

$C_{28}H_{45}N_2OCl$ requires: C, 72.96; H, 9.77; N, 6.08%.

Reaction of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (LIII) with NH_3-Zn-MeOH: 3β-chloro-5-cyano-6-oximino-5α-cholestane (CIII)

To a solution of nitrocyanide (LIII) (2 g) in ether-methanol mixture (100 ml, 1:1) containing liquor ammonia (sp. gr. 0.91, 35 ml) was added zinc dust (8 g), and the reaction mixture was continuously stirred. After the reaction was over (20-30 minutes), the suspension was filtered and filtrate was poured into water and extracted with ether as usual. Removal of the solvent and crystallization from methanol provided the desired oxime (CIII). Yield, 1.55 g; m.p.182°.

Hydrolysis of 3β-chloro-5-cyano-6-oximino-5α-cholestane (CIII): 3β-chloro-5-cyano-5α-cholestan-6-one (CVII)

A mixture of oxime (CIII) (1.0 g) in dioxane (20 ml) and hydrobromic acid (40%, 10 ml) was refluxed on a heating mantel for 24 hours by which time the reaction completed (TLC). Excess dioxane was then removed on reduced pressure and mixed with a large amount of water. The compound, thus precipitated was extracted with ether and the ethereal layer washed successively with water sodium bicarbonate (5%) and water, dried over anhyd. sodium sulphate. Removal of the solvent gave an oily residue which was crystallized from methanol to obtain the ketone (CVII). Yield, 0.70 g; m.p.147°.

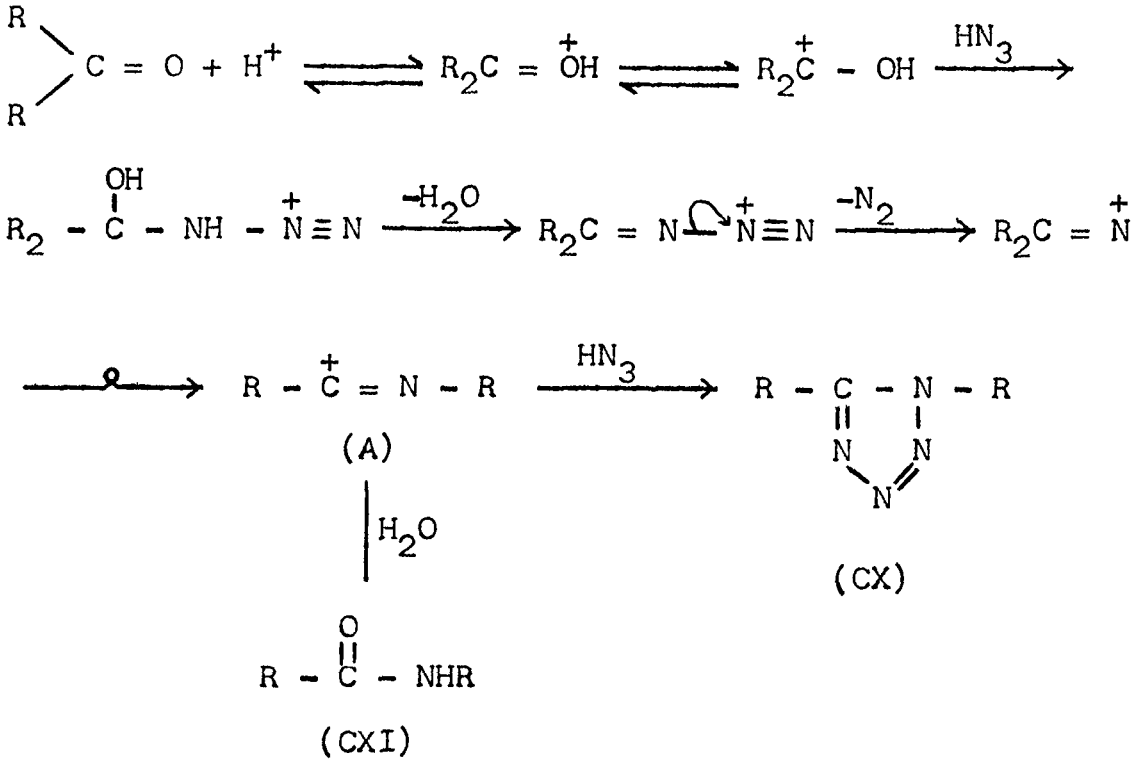
Part Three

Cyano-azasteroids

Theoretical

Tetrazoles have found important biological as well as non-biological applications[73]. Stimulant, depressant, sedative, analgesic, anticonvulsant, fungicidal, hypotensive and various other actions are exhibited by a number of tetrazoles. Metrazole which is pentamethylene tetrazole is a potent stimulant of the central nervous system. Tetrazoles have been used as binders in composite propellants, match compositions and as catalysts in polymerization. They are of use in fibre, dyestuff and taxtile industries.

With the realization of the above mentioned applications of the tetrazoles, organic chemists directed their attention towards their synthesis. The most valuable method discovered by Schmidt[74] for the synthesis of tetrazole is the rearrangement reaction between ketone and hydrazoic acid in the presence of other strong acids. Smith[75] has proposed a mechanism for this transformation of amide (lactam in the case of cyclic ketone) as a side product. Upon reacting one mole of hydrazoic acid, the ketone is converted to the intermediate imidocarbonium ion (A) which then reacts with the second mole of the hydrazoic acid to form tetrazole (CX). This combination of hydrazoic acid with imidocarbonium ion to form tetrazole competes with the reaction of imidocarbonium ion with water to form N-substituted amide (CXI).



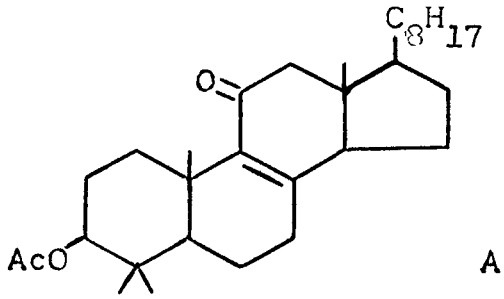
(A)

(CXI)

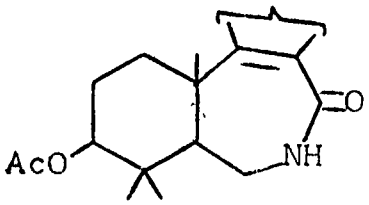
(CX)

Steroidal Tetrazoles

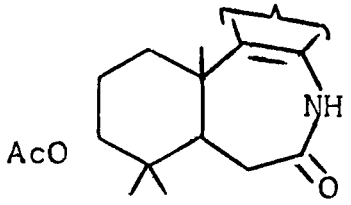
Probably the first example of the formation of tetrazole in steroid field was given by Barnes et al.[76] in 1952. They treated 7,11-dioxolanost-8-en-3β-yl acetate (CXII) with hydrazoic acid and obtained in addition to two isomeric lactams (CXIII and CXIV) a tetrazole (CXV or CXVI).



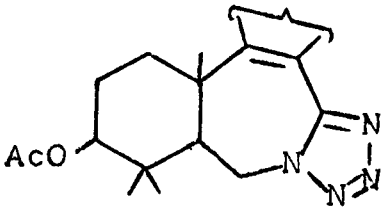
(CXII)



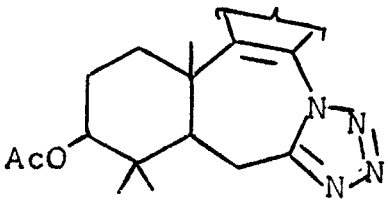
(CXIII)



(CXIV)

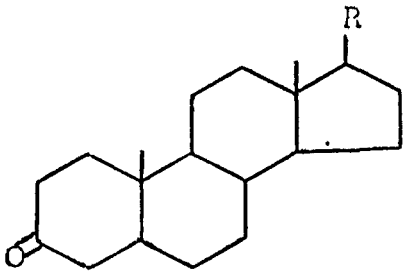


(CXV)

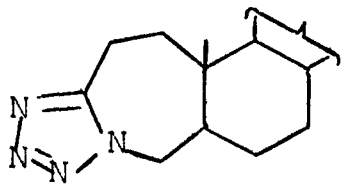


(CXVI)

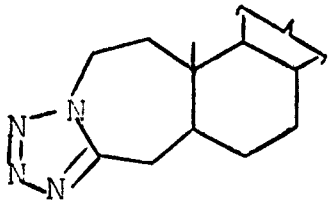
Mechoulam[77] subjected 5α-cholestan-3-one (CXVIIa) and 17β-hydroxy-5α-androstan-3-one (CXVIIb) to Schmidt reaction using excess of hydrazoic acid to afford a mixture of isomeric tetrazoles, 3-aza-A-homo[3,4-d]tetrazole (CXVIII) and 4-aza-A-homo [4,3-d]tetrazole (CXIX).



(CXVII)



(CXIX)

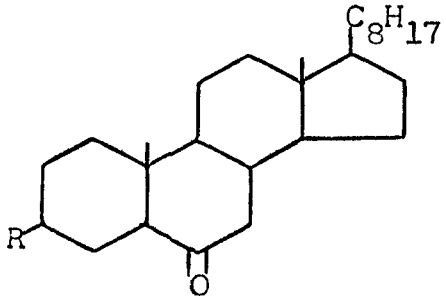


(CXVIII)

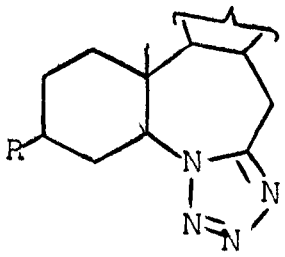
R= (a) $-C_8H_{17}$; (b) -OH

Cervantes et al.[78] reported the formation of ring-D fused tetrazoles from the reaction of 17-ketoximes with sodium azide in the presence of sulphuric acid.

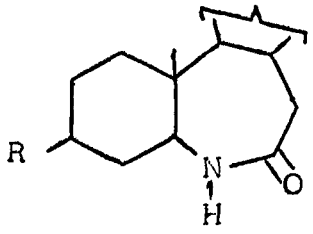
Ahmad et al.[79] when treated 6-oxosteroids (CXX) with an excess of hydrazoic acid obtained the corresponding 6-azatetrazoles (CXXI) and 6-azalactams (CXXII) only because of the more migratory aptitude of tertiary C5 relative to secondary C7.



(CXX)



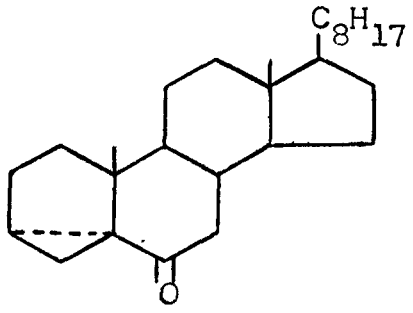
(CXXI)



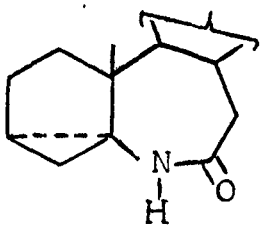
(CXXII)

R= (a) H; (b) -OAc; (c) -OH; (d) -Cl

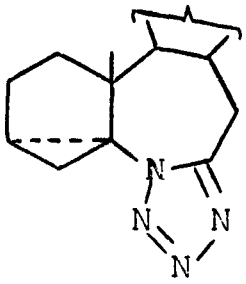
3α,5-Cyclo-5α-cholestan-6-one (CXXVIII) when subjected to Schmidt reaction gave 6-azatetrazole (CXXX) and 6-azalactam (CXXXI), while 3β-acetoxy-5-oxo-5,6-secocholestan-6-nitrile (CXXXII) was obtained from 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CXXIX)[80].



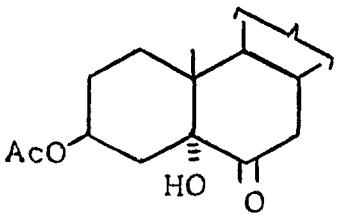
(CXXVIII)



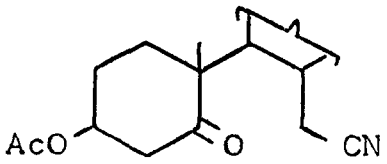
(CXXXI)



(CXXX)

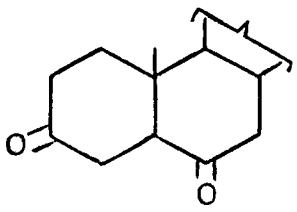


(CXXIX)

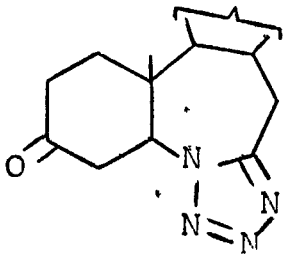


(CXXXII)

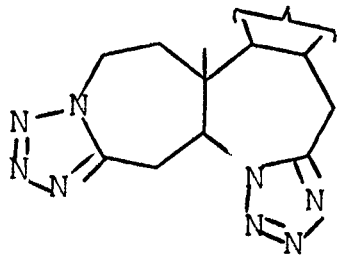
Ahmed et al.[81] treated 5α-cholestan-3,6-dione (CXXXIII) with hydrazoic acid and reported the formation of tetrazole (CXXXV) and two isomeric bis-tetrazoles (CXXXVI and CXXXVII). 5-Hydroxy-5α-cholestan-3,6-dione (CXXXIV) under similar conditions provided 4-aza-A-homo-5-hydroxy-6-oxo-5α-cholestano[3,4-d]tetrazole (CXXXVIII) and 4-aza-A-homo-3,5a-dioxo-5,6-secocholestano-6-tetrazole (CXXXIX).



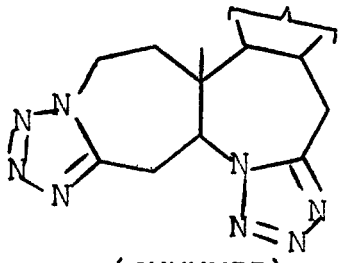
(CXXXIII)



(CXXXV)



(CXXXVI)



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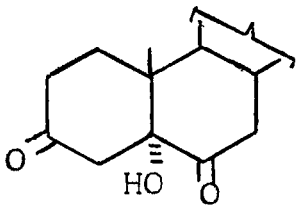
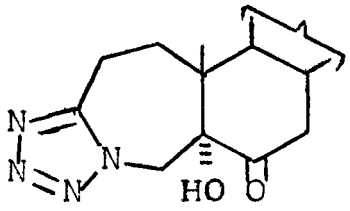
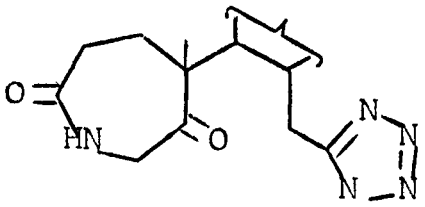


(CXXXIV)

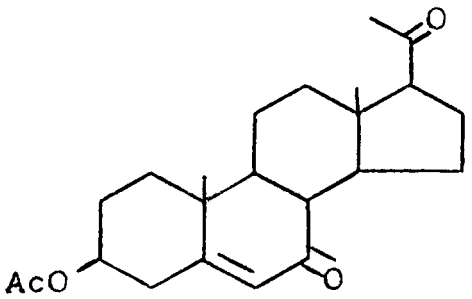


(CXXXVIII)

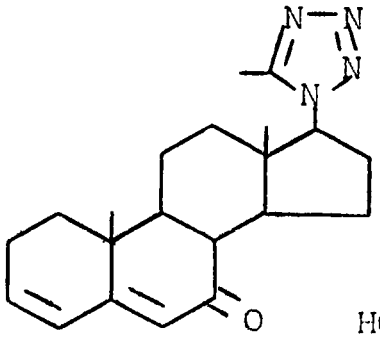


(CXXXIX)

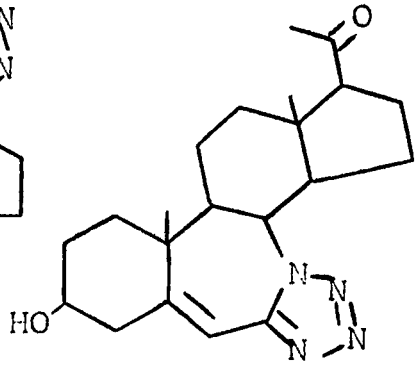
Singh et al.[82] have prepared tetrazoles (CXLI-CXLIV) by the reaction of 3β-acetoxy-pregn-5-ene-7,20-dione (CXL) with an excess of hydrazoic acid-borontrifluoride-etherate in chloroform.



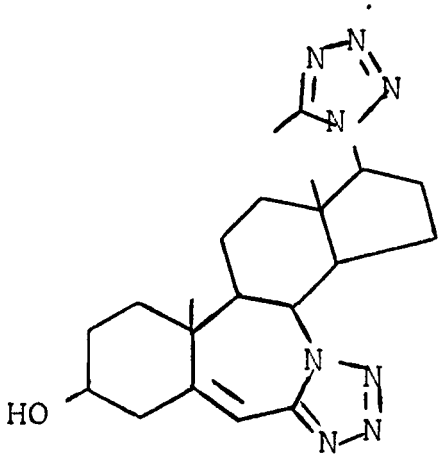
(CXL)



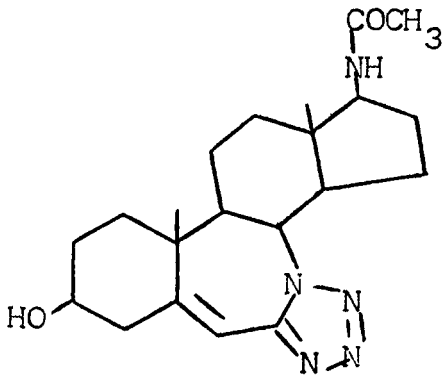
(CXLI)



(CXLII)

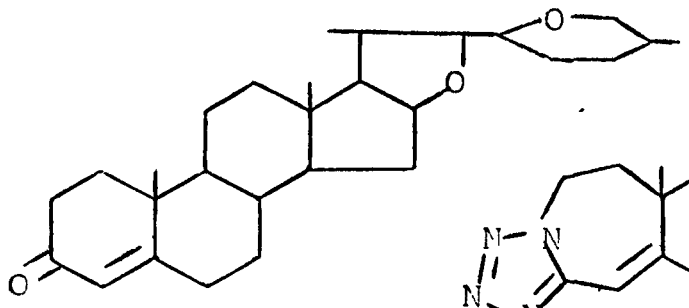


(CXLIII)

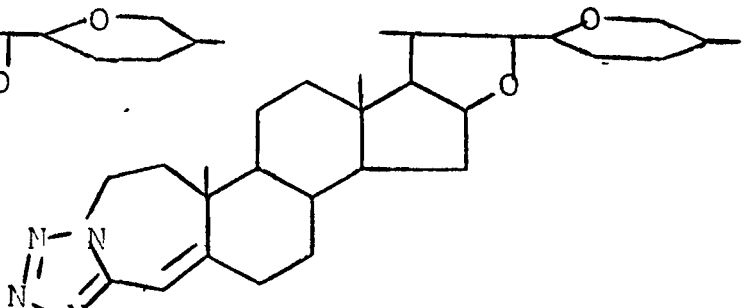


(CXLIV)

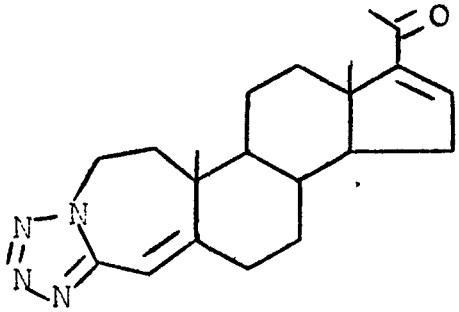
25(R)-Spirost-4-en-3-one (CXLV) on treatment with hydrazoic acid gave only 3-aza-A-homo(25R)-spirost-4a-eno[3,4-d] tetrazole (CXLVI) which on Marker degradation was converted to 3-aza-A-homopregna-4a,16-dieno[3,4-d]tetrazole-20-one (CXLVII)[83].



(CXLV)

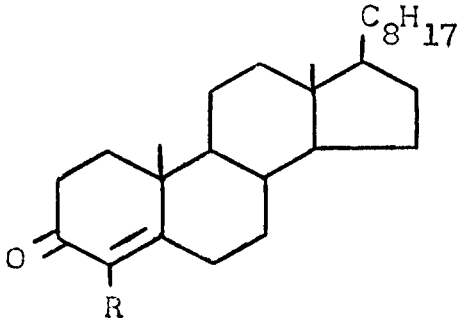


(CXLVI)

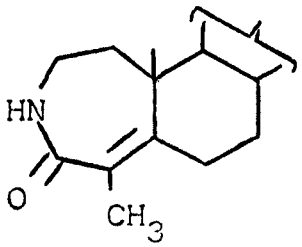


(CXLVII)

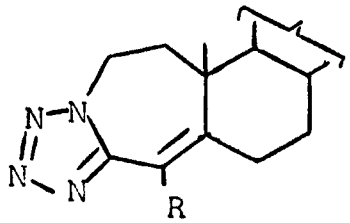
Shafiullah et al.[84] have studied the reaction of 4-methyl and 4-ethylcholest-4-en-3-one (CXLVIIIa and CXLVIIIb) respectively with HN_3-BF_3-etherate. Thus, (CXLVIIIa) when subjected to above reaction furnished 3-aza-A-homo-4a-methyl-cholest-4a-eno[3,4-d]tetrazole (CLa) and lactam (CXLIXa) while only tetrazole (CLb) was obtained in the case of (CXLVIIIb).



(CXLVIII)



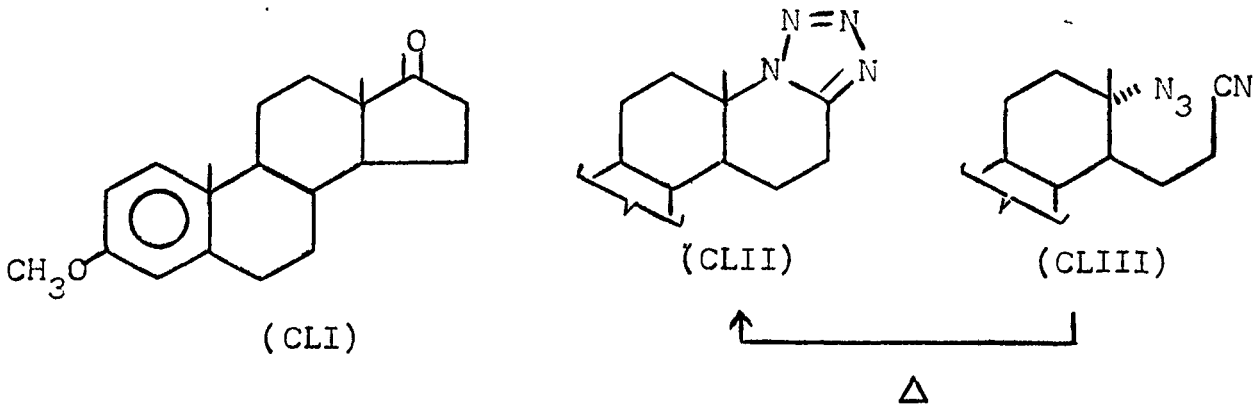
(CXLIX)



(CL)

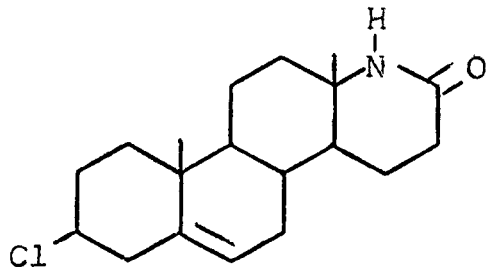
R= (a) $-CH_3$; (b) $-C_2H_5$

Singh et al.[85-87] have reported an unusual formation of azidonitrile in addition to the tetrazole by the reaction of various steroidal ketones with HN_3. For example estrone methyl ether (CLI) gave azidonitrile (CLIII) and tetrazole (CLII) under above condition. The azidonitrile (CLIII) was cyclized to tetrazole (CLII) on heating. This is claimed to be the first instance of the isolation of an azidonitrile formed under Schmidt reaction conditions and its thermal cyclization to a tetrazole.

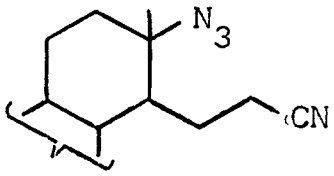


(CLI) (CLII) (CLIII)

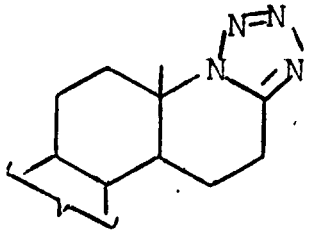
Recently Siddiqui et al.[88] have also obtained azidonitrile beside tetrazole (CLVI) in the reaction of 3β-chloroandrost-5-en-17-one (CLIV) with hydrazoic acid.



(CLIV)



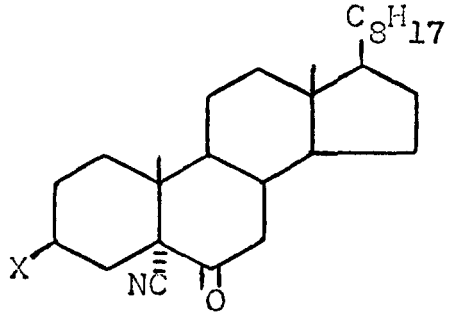
(CLV)

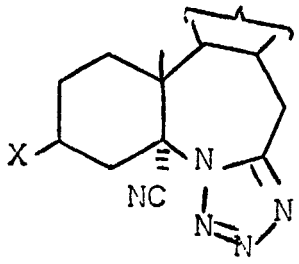


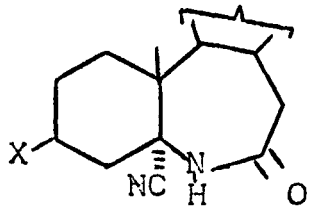
(CLVI)

Discussion

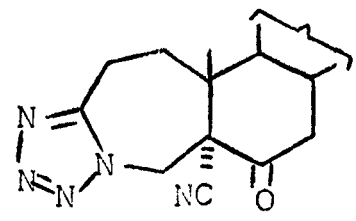
Synthesis of tetrazoles and lactams (CLVII-CLXIII)has been carried out by treating hitherto unexplored cyanoketones (CIV-CVII) with hydrazoic acid under Schmidt reaction conditions. 5-Cyano-5α-cholestane-3,6-dione (CVIII) was also treated with hydrazoic acid and borontrifluoride etherate to obtain azasteroids (CLXIV-CLXVI). Tetrazoles were found in major quantity.



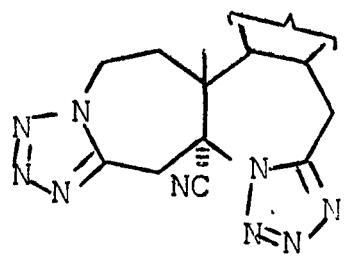




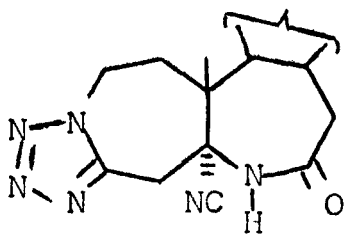
	X		X		X
(CIV)	-OH	(CLVII)	-OH	(CLXI)	-OH
(CV)	-OAc	(CLVIII)	-OAc	-	
(CVI)	-H	(CLIX)	-H	(CLXII)	-H
(CVII)	-Cl	(CLX)	-Cl	(CLXIII)	-Cl



(CLXIV)



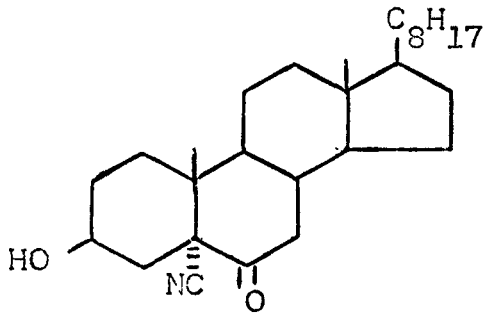
(CLXV)



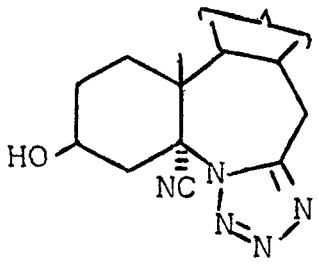
(CLXVI)

Reaction of 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV) with hydrazoic acid

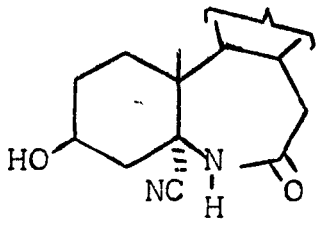
3β-Hydroxy-5-cyano-5α-cholestan-6-one (CIV) with an excess of hydrazoic acid[36] and borontrifluoride etherate as catalyst at room temperature. Work up of the reaction mixture and column chromatography over silica gel gave two products m.p.121° (major) and 235° (minor).



(CIV)



(CLVII)



(CLXI)

Characterization of the compound, m.p.121°, as 3β-hydroxy-6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLVII)

The compound, m.p.121°, gave an analysis for $C_{28}H_{45}N_5O$. Its IR spectrum exhibiting absorption bands at 3400 (OH), 2240 (C≡N), 1530 (C=N), 1430, 1340 cm^{-1} (N=N), suggested the formation of the cyanotetrazole (CLVII). The 6-aza formation of this tetrazole was based on the one proton doublet with J=15 Hz appearing at

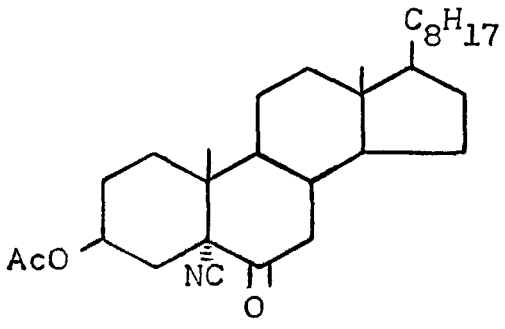
δ 3.5 which is due to the C7-proton adjacent to the C=N of the tetrazole moiety[79]. A multiplet at δ 4.00 integrating for one proton and another multiplet at δ 3.0 (exchangeable with D_2O) were due to C3-α<u>H</u> and C3-O<u>H</u> protons respectively. Methyl protons were seen at 0.92 (C10-C<u>H</u>$_3$), 0.65 (C13-C<u>H</u>$_3$), 0.63, 0.82 and 0.88 (remaining methyl protons).

<u>Characterization of the compound, m.p. 235° as 3β-hydroxy-6-aza-B-homo-5-cyano-5α-cholestan-7-one (CLXI)</u>

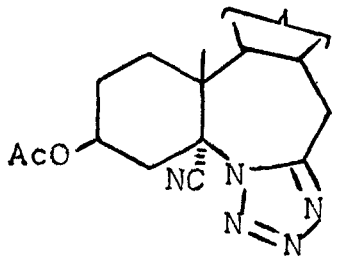
The compound, m.p. 235° analysing for $C_{28}H_{46}N_2O_2$ and displaying absorption bands in its IR spectrum at 3480, 3400, 3200 for OH and NH stretching frequencies in conjunction with bands at 2230 (C≡N) and 1650 (CO) indicated the formation of cyanolactam (CLXI). PMR spectrum of this product gave a one-proton multiplet at δ 7.00, found to be exchangeable with D_2O, was ascribable for NH of lactam. A multiplet with W1/2=21 Hz at δ 3.80 is assignable to the C3-α<u>H</u>. Another multiplet integrating for one proton (δ 3.30) exchangeable with D_2O was assigned to C3-O<u>H</u> proton. Methyl protons were observed at δ 0.90 (C10-C<u>H</u>$_3$), 0.67 (C13-C<u>H</u>$_3$), 0.88 and 0.80 (other methyl protons).

Reaction of 3β-acetoxy-5-cyano-5α-cholestan-6-one (CV) with an excess of hydrazoic acid

Reaction of cyanoketone (CV) with hydrazoic acid followed by usual work up and crystallization afforded a compound, m.p.128°.



(CV)



(CLVIII)

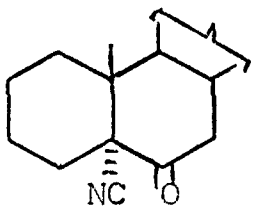
Characterization of the compound, m.p.128° as 3β-acetoxy-6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLVIII)

The compound, m.p.128°, analysing for $C_{30}H_{47}N_5O_2$ exhibited in its IR spectrum absorption bands at 2220 (C≡N), 1740 (O-CO-CH_3), 1520 (C=N), 1440 and 1330 cm^{-1} (N=N), which indicated the formation of tetrazole. PMR spectrum showed a multiplet at δ 5.14 integrating for one proton which is ascribable to C3-αH. A one-proton doublet with J=15 Hz at δ 3.6, a characteristic for 6-azatetrazoles[79] to one of the C7-protons. Another multiplet

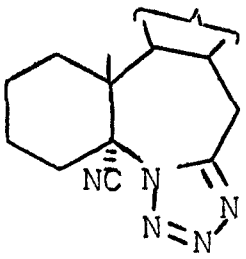
centred at δ 3.0 for one-proton was due to the other C7-proton. A sharp singlet integrating for 3 protons appearing at δ 2.10 was due to the protons of acetate group at C3. Methyl signals were observed at δ 0.92 ($C10-CH_3$), 0.64 ($C13-CH_3$), 0.88 and 0.81 (remaining methyl protons). This reaction, however, did not furnish the corresponding lactam. Only tetrazole (CLVIII) was isolated from the Schmidt reaction of cyanoketone (CV).

Reaction of 5-cyano-5α-cholestan-6-one (CVI) with an excess of hydrazoic acid

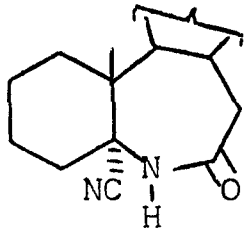
5-Cyano-5α-cholestan-6-one (CVI) was treated with an excess of hydrazoic acid in the presence of borontrifluoride etherate as catalyst at room temperature. Usual work up of the reaction mixture and column chromatography over silica gel provided two compounds with m.p.140° in major proportion as compared to the product which melted at 85°.



(CVI)



(CLIX)



(CLXII)

Characterization of the compound, m.p.140°, as 6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLIX)

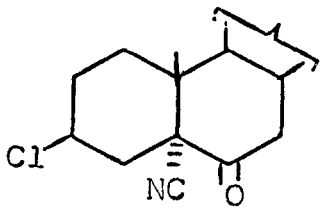
The compound, m.p.140°, analysed for $C_{28}H_{45}N_5$ and thus indicated the probability of a tetrazole moiety in the product. Its IR spectrum showed absorption band at 2235 (C≡N), 1520 (C=N), and 1420, 1380 cm^{-1} (N=N). NMR spectrum giving a doublet (J=15 Hz) at δ 3.5 for one of the C7-protons indicated the formation of 6-azatetrazole[79]. A multiplet centred at δ 2.83 for one proton could be assigned to another C7-proton. Methyl signals appeared at δ 0.91 (C10-CH_3), 0.60 (C13-CH_3), 0.80 and 0.75 (remaining methyl protons).

Characterization of the compound, m.p.85°, as 6-aza-B-homo-5-cyano-5α-cholestan-7-one (CLXII)

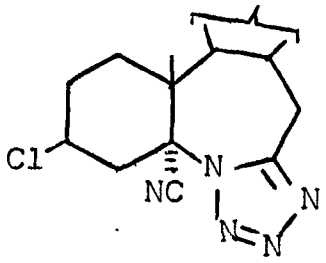
The compound, m.p.85°, was analysed for $C_{28}H_{46}N_2O$. This elemental analysis indicated the formation of lactam which was supported by appearance of an absorption band at 1660 cm^{-1} (amide II band) in its IR spectrum. A broad band at 3300-3200 and a sharp medium band at 2230 cm^{-1} were compatible with NH-CO and C≡N stretching frequencies respectively. The PMR spectrum of this product showed a multiplet at δ 6.70 integrating for one proton and found to be exchangeable with D_2O, was due to NH proton of lactam. Methyl protons appeared at δ 0.90 (C10-CH_3), 0.60 (C13-CH_3), 0.80 and 0.70 (remaining methyl protons).

Reaction of 3β-chloro-5-cyano-5α-cholestan-6-one (CVII) with an excess of hydrazoic acid

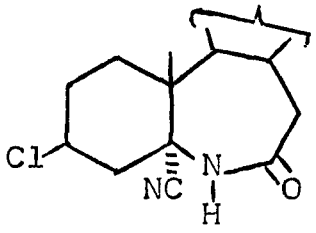
The reaction of the compound (CVII) with an excess of hydrazoic acid was performed in the usual manner. Work up of the reaction mixture and column chromatography over silica gel furnished two products m.ps.211° (major) and 128° (minor).



(CVII)



(CLX)



(CLXIII)

Characterization of the compound, m.p.211°, as 3β-chloro-6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLX)

The compound, m.p.211°, was analysed for $C_{28}H_{44}N_5Cl$ and this analysis indicated the formation of a tetrazole. The IR spectrum of this compound showed absorption bands at 2230, 1540 and 1440, 1350 cm^{-1} which correspond to C≡N, C=N and N=N stretching frequencies. PMR spectrum supported the structure (CLX) It exhibited a doublet (J=15 Hz) for one proton at δ 3.50, assign-

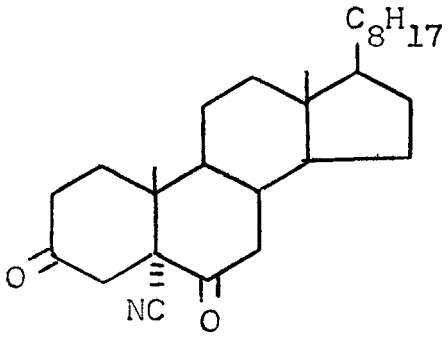
able to a C7-proton, a characteristic for the 6-azatetrazoles[79]. Methyl protons appeared at δ 0.91 (C10-CH_3), 0.65 (C13-CH_3), 0.82 and 0.68 (remaining methyl protons).

Characterization of the compound, m.p.128°, as 3β-chloro-6-aza-B-homo-5-cyano-5α-cholestan-7-one (CLXIII)

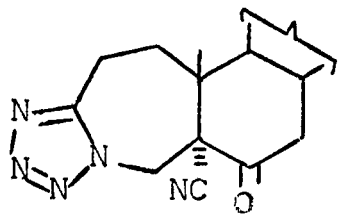
The compound, m.p.128°, analysing for $C_{28}H_{45}N_2OCl$ showed absorption bands in its IR spectrum at 3280, 3180 (NH), 1670 (C=O), which indicate this product to be a lactam. PMR spectrum showing a broad signal for one proton at δ 7.30, found exchangeable with D_2O could be assigned to NH of lactam. A multiplet with W1/2=20 Hz at δ 4.17 was due to the C3-αH. Methyl protons were observed at δ 0.98 (C10-CH_3), 0.63 (C13-CH_3), 0.85 and 0.90 (remaining methyl protons).

Reaction of 5-cyano-5αcholestan-3,6-dione (CVIII) with an excess of hydrazoic acid

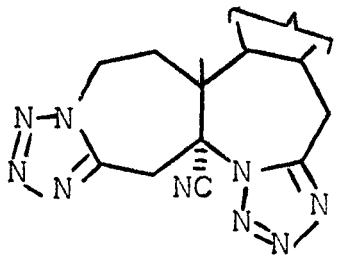
A similar reaction of cyanodiketone (CVIII) with an excess of hydrazoic acid and upon usual work up and column chromatography afforded three products m.ps.240° (CLXIV), 255° (CLXV) and 223° (CLXVI).



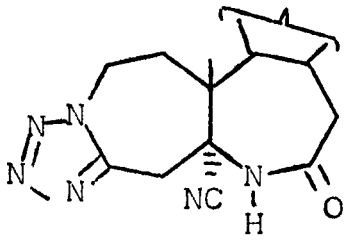
(CVIII)



(CLXIV)



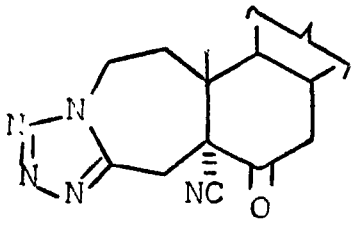
(CLXV)



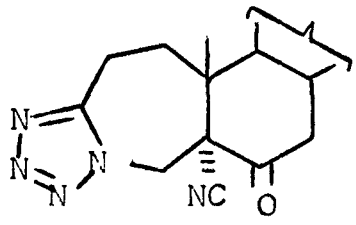
(CLXVI)

Characterization of the compound, m.p.240° as 4-aza-A-homo-5-cyano-6-oxo-5α-cholestano[4,3-d]tetrazole (CLXIV)

The compound, m.p.240° analysing for $C_{28}H_{43}N_5O$ suggested the formation of tetrazole. IR spectrum of this product showed bands at 2230 (C≡N), 1530 (C=N) and 1420, 1360 cm^{-1} (N=N) and thus suggested the formation of cyanotetrazole. A strong band at 1730 cm^{-1} can unambiguously be assigned to the unreacted C6-carbonyl group. The cyanotetrazole which involved the C3-oxo group may have either 3-aza-(X) or 4-aza-(Y) structures.

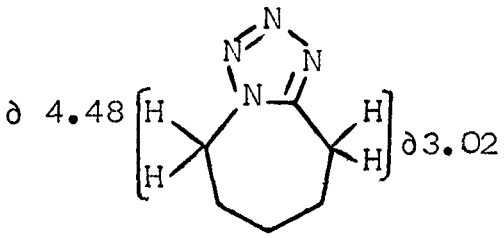


(X)



(Y)

The distinction between these isomers can be made on the basis of the report by Maio and Permmutti[89] that PMR spectrum of the tetrazole of the type (Z) exhibits a two proton multiplet at ð 4.48 which is ascribable to the methylene group directly attached to the ring nitrogen atom and another two proton multiplet at ð 3.02 is due to the methylene group adjacent to C=N of the tetrazole moiety.



(Z)

PMR spectrum of this compound exhibited a couple of doublets (J=16 Hz) at ð 5.2 and 4.43 each integrating for one proton (non-equivalent protons showing gem coupling near assymetric centre) which could be assigned to C4a-2H. These two doublets with above values are possible in structure (Y). The multiplet at

δ 3.50 for two protons (C2-2H) also favours the structure (Y). In the alternative structure (X) the C2-protons would appear around δ 4.48 as multiplet and C4a-2H as doublet of a doublet ~ δ 3.02. On the basis of above discussion compound m.p. 240°, has been characterized as 4-aza-A-homo-5-cyano-6-oxo-5α-cholestano [4,3-d]tetrazole (CLXIV).

Characterization of the compound m.p.255° as 3,6-diaza-A,B-bis-homo-5-cyano-5α-cholestano[3,4-d][6,7-d]bistetrazole (CLXV)

The compound melting at 255° was analysed for $C_{28}H_{43}N_9$ which corresponds to a bistetrazole. The IR spectrum of this product exhibited a strong band at 1540 cm^{-1} for the stretching frequency C=N of the tetrazole. Other bands seen at 2230, 1450 cm^{-1} are compatible with C≡N and N=N functions. Its PMR spectrum gave a two proton multiplet at δ 4.6 for the C2-2H protons adjacent to inserted nitrogen and another multiplet at δ 3.55 integrating for 4 protons could be assigned to C4 and C7 protons, confirming the 3-aza assignment of ring A tetrazole. The 6-aza assignment of ring B tetrazole is favourable partly due to the consideration that C5-C6 bond, a tertiary one, has more migratory aptitude in comparison to the secondary C6-C7. Further, the 4 proton multiplet at δ 3.4 is possible only in 6-aza structure (CLXV). The alternative 7-aza-could have exhibited a 4 protons multiplet at ~ δ 4.5. On the basis of above discussion the compound is

characterized as 3,6-diaza-A,B-bishomo-5-cyano-5α-cholestano [3,4-d][6,7-d]bistetrazole (CLXV).

Characterization of the compound, m.p.223°, as 3,6-diaza-A,B-bis-homo-7-oxo-5-cyano-5α-cholestano[3,4-d]tetrazole (CLXVI)

The compound, m.p.223° was analysed for $C_{28}H_{44}N_6O$ and thus suggested the formation of a lactam tetrazole. The IR spectrum of this compound showed strong absorption at 3350 cm^{-1} for NH stretching of lactam and other bands at 2240, 1650, 1530, 1430 and 1380 cm^{-1} which are compatible with C≡N, C=N and N=N stretching frequencies. Its PMR spectrum gave a multiplet for 1H at δ 7.50 which was found to be exchangeable with D_2O (NH-CO proton). A multiplet for two protons at δ 4.65 assignable to C2-2H and a dist. doublet at δ 3.35 for C4a-2H, suggested 3-aza tetrazole in the product (CLXVI).

A notable point in the IR spectra of 6-aza tetrazoles and lactams is the appearance of a very weak cyanide band. This is perhaps due to the presence of nitrogen at the same carbon atom as the nitrile which is likely to considerably reduce the cyanide band intensity analogous to the inserted oxygen[90].

Experimental

Reaction of 3β-hydroxy-5-cyano-5α-cholestan-6-one (CIV) with an excess of hydrazoic acid: 3β-hydroxy-6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLVII) and 3β-hydroxy-6-aza-B-homo-5-cyano-5α-cholestan-7-one (CLXI)

To a cold solution of hydrazoic acid in benzene (50 ml) was added borontrifluoride etherate (2 ml freshly distilled). To this a solution of cyanoketone (CIV) (2.0 g) in benzene (25 ml) was added and the mixture allowed to stand at room temperature for 24 hours. Benzene was then removed under reduced pressure and the residue dissolved in chloroform. The chloroform solution was washed successively with water, sodium bicarbonate solution (~5%) and water, dried over anhyd. sodium sulphate and filtered. Removal of the solvent and crystallization from ethanol afforded the cyanotetrazole (CLVII). Yield, 1.65 g; m.p.121°.

IR(KBr) : ν_{max} 3400 (br, OH), 2240 (C≡N), 1530 (C=N), 1430 and 1340 cm^{-1} (N=N).

PMR($CDCl_3$) : δ 4.00 (m, W1/2=18 Hz, 1H, C3-α<u>H</u>), 3.5 (d, J=15 Hz, 1H, C7-<u>H</u>), 3.0 (br,s, 1H, exchangeable with D_2O, C3-O<u>H</u>), 2.8 (d-like, 1H, C7-<u>H</u>), 0.92 (s, 3H, C10-C<u>H</u>$_3$), 0.65 (s, 3H, C13-C<u>H</u>$_3$), 0.88, 0.82 and 0.63 (remaining methyl protons).

Analysis Found : C, 72.07; H, 9.58; N, 15.04;

$C_{28}H_{45}N_5O$ requires : C, 71.95; H, 9.64; N, 14.99%.

The mother liquor containing a mixture of two products was chromatographed over a silica gel column (20 g; BDH, Bombay). Elution with benzene-chloroform (15:1) gave the cyanotetrazole (CLVII) m.p.121°, yield 0.2 g.

Continued elution with benzene-chloroform (10:1) on crystallization from methanol afforded the lactam (CLXI) as shining white crystals. Yield, 0.12 g; m.p.235°.

IR(KBr) : ν_{max} 3480, 3400, 3200 (OH, NH), 2230 (C≡N) and 1650 cm^{-1} (CO).

PMR($CDCl_3$ + $DMSO-d_6$) : δ 7.00 (m, 1H, exchangeable with D_2O, N<u>H</u>), 3.80 (m, W1/2=21 Hz, 1H, C3-α<u>H</u>), 3.30 (m, 1H, exchangeable with D_2O, C3-O<u>H</u>), 0.90 (s, 3H, C10-C<u>H</u>$_3$), 0.67 (s, 3H, C13-C<u>H</u>$_3$), 0.88 and 0.80 (remaining methyl protons).

Analysis Found : C, 76.11; H, 10.48; N, 6.26;

$C_{28}H_{46}N_2O_2$ requires : C, 76.02; H, 10.41; N, 6.33%.

Reaction of 3β-acetoxy-5-cyano-5α-cholestan-6-one (CV) with an excess of hydrazoic acid: 3β-acetoxy-6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLVIII)

3β-Acetoxy-5-cyano-5α-cholestan-6-one (CV) (2.0 g) was treated with hydrazoic acid-borontrifluoride etherate in the usual manner. Evaporation of the solvent and crystallization of the residue from alcohol afforded the cyanotetrazole (CLVIII) as the sole product of this reaction. Yield, 1.80 g; m.p.128°.

IR(KBr) : ν_{max} 2220 (C≡N), 1740 (-OCOCH$_3$), 1520 (C=N), 1440 and 1330 cm^{-1} (N=N).

PMR($CDCl_3$) : δ 5.14 (m, W1/2=22 Hz, 1H, C3-α<u>H</u>), 3.60 (d, J=15 Hz, 1H, C7-<u>H</u>), 3.00 (m, 1H, C7-<u>H</u>), 2.10 (s, 3H, C<u>H</u>$_3$COO-), 0.92 (s, 3H, C10-C<u>H</u>$_3$), 0.64 (s, 3H, C13-C<u>H</u>$_3$), 0.88, and 0.81 (remaining methyl protons).

Analysis Found : C, 70.66; H, 9.17; N, 13.68;

$C_{30}H_{47}N_5O_2$ requires : C, 70.73; H, 9.23; N, 13.75%.

Reaction of 5-cyano-5α-cholestan-6-one (CVI) with an excess of hydrazoic acid: 6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLIX) and 6-aza-B-homo-5-cyano-5α-cholestan-7-one (CLXII)

To a cold solution of hydrazoic acid (50 ml) in benzene, was added borontrifluoride etherate (2 ml, freshly distilled). To

this, a solution of (CVI) (2.0 g) in benzene (25 ml) was added and the mixture allowed to stand at room temperature for 24 hours. Benzene was then removed under reduced pressure and the residue dissolved in chloroform. The chloroform solution was washed successively with water, sodium bicarbonate solution (~5%) and water. This solution was dried over anhydrous sodium sulphate and filtered. Evaporation of the solvent and crystallization from ethanol afforded the cyanotetrazole (CLIX). Yield, 1.6 g; m.p. 140°.

IR(KBr) : ν_{max} 2235 (C≡N), 1520 (C=N), 1420 and 1380 cm^{-1} (N=N).

PMR($CDCl_3$) : δ 3.5 (d, J=15 Hz, 1H, C7-H), 2.83 (m, 1H, C7-H), 0.91 (s, 3H, C10-CH_3), 0.60 (s, 3H, C13-CH_3), 0.80 and 0.75 (remaining methyl protons).

Analysis Found : C, 74.41; H, 10.09; N, 15.47;

$C_{28}H_{45}N_5$ requires : C, 74.50; H, 9.98; N, 15.52%.

The mother liquor collected from the filter flask was concentrated to an oily residue and chromatographed on a silica gel column (20 g; BDH, Bombay). Elution with benzene-chloroform (20:1) gave tetrazole (CLIX) (crystallized from alcohol), yield, 0.15 g; m.p. 140°.

Elution with benzene-chloroform (15:1) furnished the cyanolactam (CLXII) (crystallized from methanol). Yield, 0.10 g; m.p. 85°.

IR(KBr) : ν_{max} 3300-3200 (NH), 2230 (C≡N) and 1660 cm^{-1} (CO).

PMR($CDCl_3$) : δ 6.70 (m, 1H, exchangeable with D_2O, N<u>H</u>), 0.90 (s, 3H, C10-C<u>H</u>$_3$), 0.60 (s, 3H, C13-C<u>H</u>$_3$), 0.80 and 0.70 (other methyl protons).

Analysis Found : C, 78.76; H, 10.72; N, 6.51;

$C_{28}H_{46}N_2O$ requires : C, 78.87; H, 10.80; N, 6.57%.

<u>Reaction of 3β-chloro-5-cyano-5α-cholestan-6-one (CVII) with an excess of hydrazoic acid: 3β-chloro-6-aza-B-homo-5-cyano-5α-cholestano[6,7-d]tetrazole (CLX) and 3β-chloro-6-aza-B-homo-5-cyano-5α-cholestan-7-one (CLXIII)</u>

Reaction of (CVII) (2 g) in the usual manner, subsequent work up and crystallization from alcohol gave cyanotetrazole (CLX), m.p.211°, yield 1.5 g.

IR(KBr) : ν_{max} 2230 (C≡N), 1540 (C=N), 1440, 1350 (N=N) and 750 cm^{-1} (C-Cl).

PMR($CDCl_3$) : δ 4.17 (m, W1/2=20 Hz, 1H, C3-α<u>H</u>), 3.50 (d, J=15 Hz, 1H, C7-<u>H</u>), 3.17 (m, 1H, C7-H), 0.91 (s, 3H, C10-C<u>H</u>$_3$), 0.65 (s, 3H, C13-C<u>H</u>$_3$), 0.82 and 0.68 (other remaining methyl protons).

Analysis Found : C, 69.28; H, 8.98; N, 14.36;

$C_{28}H_{44}N_5Cl$ requires : C, 69.21; H, 9.06; N, 14.42%.

The mother liquor collected from the filter flask was concentrated to get an oily residue which was chromatographed over a silica gel column (30 g; BDH, Bombay). Elution with benzene-chloroform (25:1) afforded on crystallization from ethanol, shining crystals of cyanotetrazole (CLX). Yield, 0.12 g; m.p.211°.

Further elution with benzene-chloroform (18:5) yielded the cyanolactam (CLXIII) (crystallized from methanol). Yield, 0.15 g; m.p.128°.

IR(KBr) : ν_{max} 3280-3180 (NH), 2230 (C≡N) and 1670 cm^{-1} (CO).

PMR($CDCl_3$) : δ 4.17 (m, W1/2=20 Hz, 1H, C3-α<u>H</u>), 7.30 (br,s, 1H, N<u>H</u>, exchangeable with D_2O), 0.98 (s, 3H, C10-C<u>H</u>$_3$), 0.63 (s, 3H, C13-C<u>H</u>$_3$), 0.90 and 0.85 (remaining methyl protons).

Analysis Found : C, 72.88; H, 9.84; N, 6.01;

$C_{28}H_{45}N_2OCl$ requires : C, 72.96; H, 9.77; N, 6.08%.

Reaction of 5-cyano-5α-cholestane-3,6-dione (CVIII) with an excess of hydrazoic acid: 4-aza-A-homo-5-cyano-6-oxo-5α-cholestano[4,3-d] tetrazole (CLXIV), 3,6-diaza-A,B-bishomo-5-cyano-5α-cholestano [3,4-d][6,7-d]bistetrazole (CLXV), 3,6-diaza-A,B-bishomo-7-oxo-5-cyano-5α-cholestano[3,4-d]tetrazole (CLXVI)

The reaction of cyanodiketone (CVIII) (2.0 g) with hydrazoic acid and borontrifluoride etherate as catalyst was effected in the usual fashion. Usual work up and crystallization from alcohol gave the monotetrazole (CLXIV). Yield, 1.1 g; m.p.240°.

IR(KBr) : ν_{max} 2230 (C≡N), 1730 (C6-CO), 1530 (C=N), 1420 and 1360 cm^{-1} (N=N).

PMR($CDCl_3$) : δ 5.2 (d, J=16 Hz, 1H, C4a-H), 4.43 (d, J=16 Hz, 1H, C4a-H), 3.50 (m, 2H, C2-2H), 1.12 (s, 3H, C10-CH_3), 0.70 (s, 3H, C13-CH_3), 0.93 and 0.82 (remaining methyl protons).

Analysis Found : C, 72.35; H, 9.18; N, 14.94;

$C_{28}H_{43}N_5O$ requires : C, 72.26; H, 9.25; N, 15.05%.

The mother liquor was concentrated when an oily residue was obtained, which was found to contained a mixture of three products. Elution with benzene-chloroform (20:4) gave cyanobis-tetrazole (CLXV). Yield, 0.47 g; m.p.255°.

IR(KBr) : ν_{max} 2230 (C≡N), 1540 (C=N), 1450, 1380 cm^{-1} (N=N).

PMR($CDCl_3$) : δ 4.6 (m, 2H, C2-2H), 3.55 (m, 4H, C4a-2H and C7-2H), 1.1 (s, 3H, C10-CH_3), 0.65 (s, 3H, C13-CH_3), 0.95 and 0.88 (remaining methyl protons).

Analysis Found : C, 66.59; H, 8.42; N, 24.84;

$C_{28}H_{43}N_9$ requires : C, 66.53; H, 8.51; N, 24.95%.

Further elution with benzene-chloroform (1:1) afforded the lactam tetrazole (CLXVI) (from methanol). Yield, 0.10 g; m.p.223°.

IR(KBr) : ν_{max} 3350 (NH), 2240 (C≡N), 1650 (C=O), 1530 (C=N), 1430 and 1380 cm^{-1} (N=N).

PMR($CDCl_3$) : δ 7.50 (m, 1H, exchangeable with D_2O, NH), 4.65 (m, 2H, C2-2H), 3.35 (dist. d, J=15 Hz, C4a-2H), 1.05 (s, 3H, C10-CH_3), 0.7 (s, 3H, C13-CH_3), 0.98, 0.85 (remaining methyl protons).

Analysis Found : C, 69.89; H, 9.09; N, 17.41;

$C_{28}H_{44}N_6O$ requires : C, 70.00; H, 9.17; N, 17.50%.

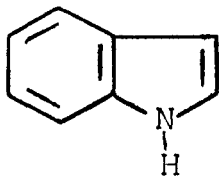
Part Four

Synthesis of Indole Dimers

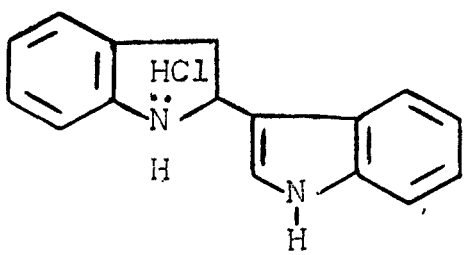
Theoretical

Indole derivatives with a lot of therapeutic properties[91-96], stimulated extensive research and resulted in the preparation of variety of heterocyclic compounds. Reaction in indole normally occurs in the position-3 or 1 because of the high electron density at these centres. Substitution at position-3 in accordance with aromatic electrophilic substitution is well known.

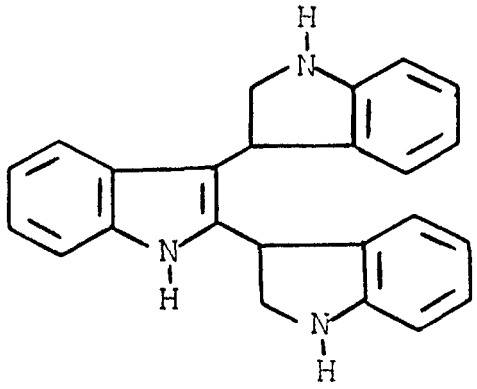
Indole is highly sensitive towards acids[97] and leads to dimerization or trimerization when subjected to react with acid depending on the conditions. Dimer hydrochloride is formed in aprotic solvents with dry hydrochloric acid[97-99] whereas aqueous media leads to dimer (CLXVIII) or trimer (CLXIX) or both[100]. Due to this in reactions of indole, the possibility of its dimerization/ trimerization borne into mind. To achieve some desired modification on a single molecule it is necessary to check their formation by varying the reaction conditions. Various reactions where two or more indole units are combined together, are described.



(CLXVII)

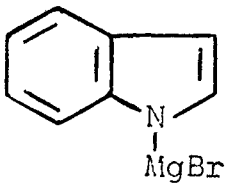


(CLXVIII)

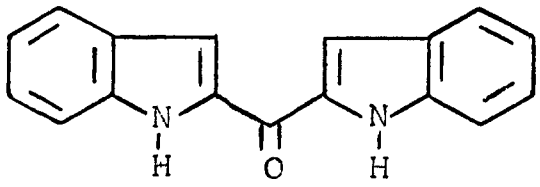


(CLXIX)

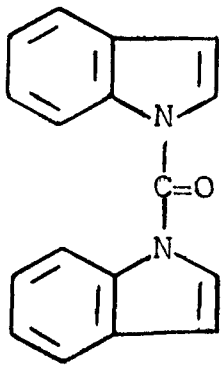
The reaction of indole magnesium bromide (CLXX) with phosgene was first reported by Oddo and Mingoia[101]. They have shown the formation of several carbonyl dimeric indoles (CLXXI-CLXXIV). Latter Bergman et al.[102] have reported carbonyl polymeric derivatives of indoles (CLXXII-CLXXVI) by repeating the reaction of indole magnesium bromide (CLXX) with phosgene in ether.



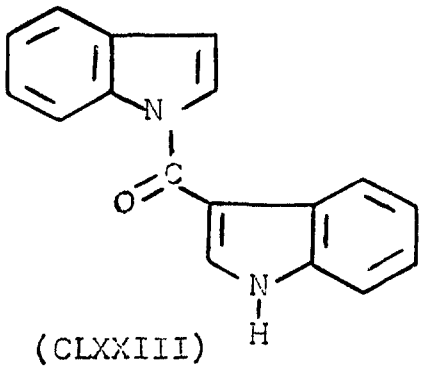
(CLXX)



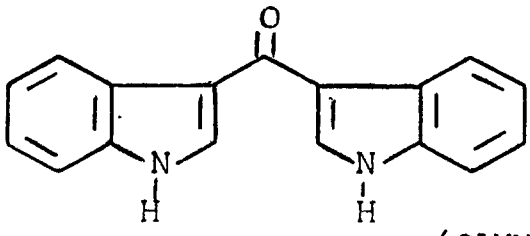
(CLXXI)



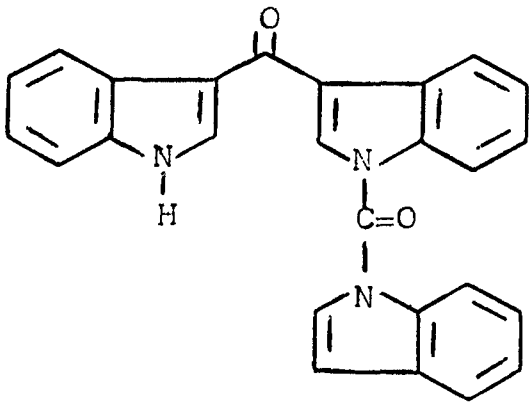
(CLXXII)



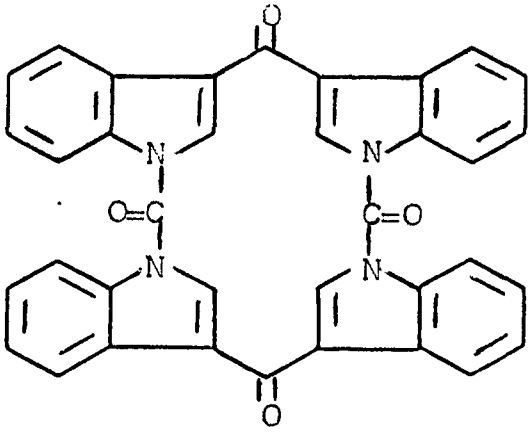
(CLXXIII)



(CLXXIV)

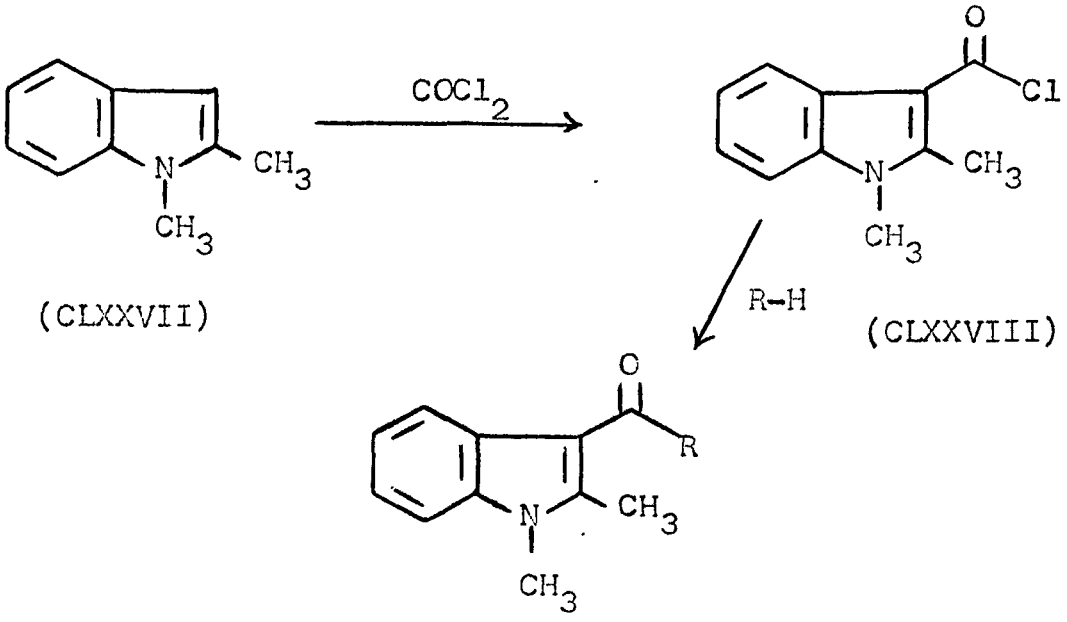


(CLXXV)



(CLXXVI)

1,2-Dimethylindole on treatment with phosgene in toluene afforded carbonyl chloride (CLXXVII)[102]. From this compound a number of derivatives (CLXXIXa-e) were obtained by replacing chlorine with different nucleophiles.

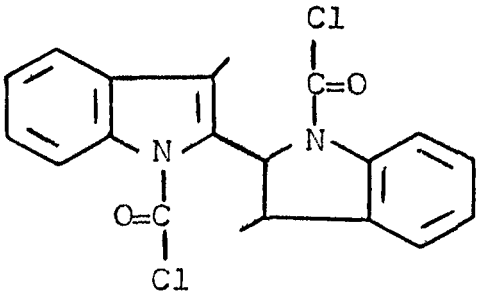


(CLXXVII) (CLXXVIII)

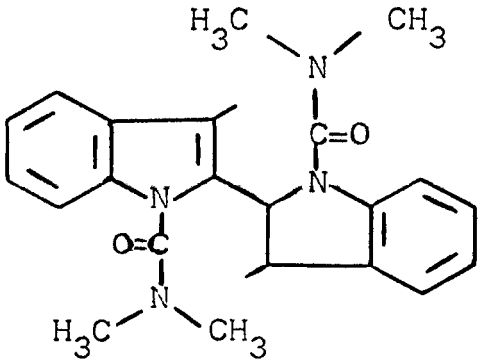
(CLXXIXa-e)

R= (a) $-OC_2H_5$, (b) $-NH_2$, (c) $-N(CH_3)_2$, (d) $-NH-NH_2$ and (e) -OH etc.

They[102] have also reported the dimerization of 3-methylindole. The reaction of 3-methylindole with phosgene in dioxane gave product (CLXXX), isolated as the N,N-dimethyl-amide derivative (CLXXXI).

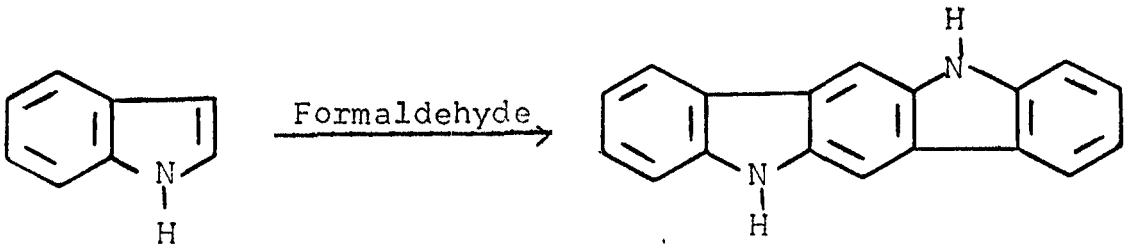


(CLXXX)



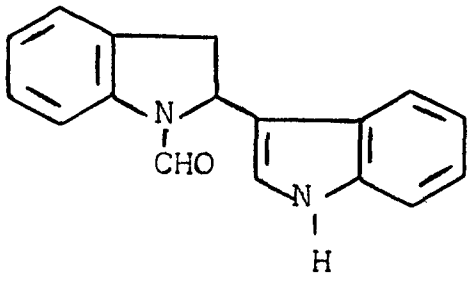
(CLXXXI)

Condensation of indole and formaldehyde in the presence of a strong catalyst afforded indole[3,2-b]carbazole (CLXXXII)[103] [provided that air, light and an aromatic ketone (sensitizer) are present].

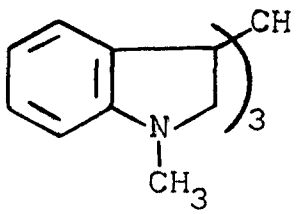


(CLXVII) (CLXXXII)

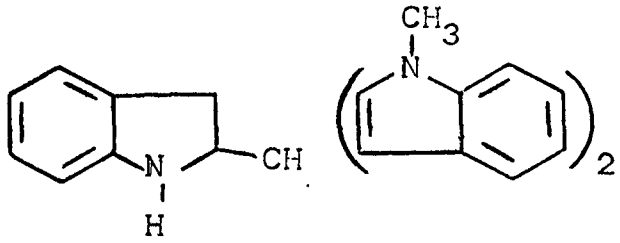
Bergman[104] carried out the reaction of indole with acetic-formic anhydride to yield indole(3)-1-formylindoline(2) (CLXXXIII). The reaction of 1-methylindole and 2-methylindole afforded products (CLXXXIV and CLXXXV) with the same reagent.



(CLXXXIII)

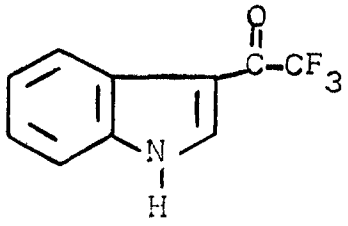


(CLXXXIV)

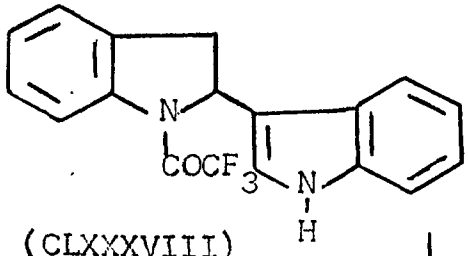


(CLXXXV)

Cipiciani et al.[105] synthesised 3-trifluoroacetylindole (CLXXXVI), N-trifluoroacetylindole (CLXXXVII) and N-trifluoroacetyl-2-(3-indolyl)-indoline (CLXXXVIII) by the reaction of trifluoroacetic acid with indole. Under basic conditions compound (CLXXXVIII) afforded known 2(3'-indolyl)indoline (CLXVIII).

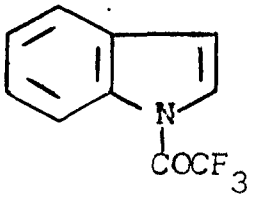


(CLXXXVI)

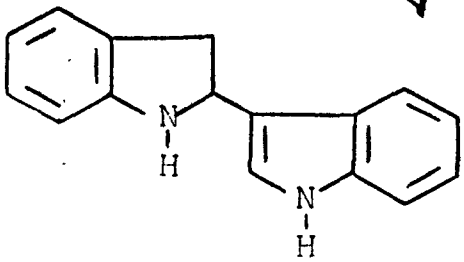


(CLXXXVIII)

KOH

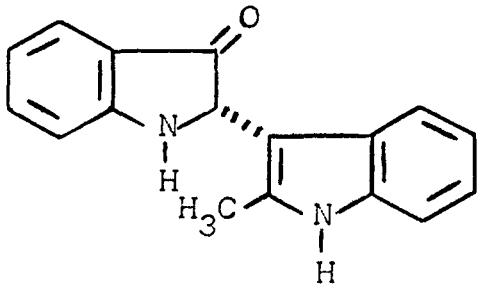


(CLXXXVII)

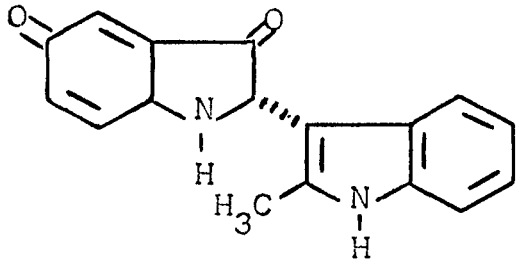


(CLXVIII)

Treatment of 2-methylindole with potassium nitrodisulphonate [$ON(SO_3K)_2$] at pH 3.5-4.0 yielded product (CLXXXIX) whereas at pH-7 compound (CXC) was obtained[106].

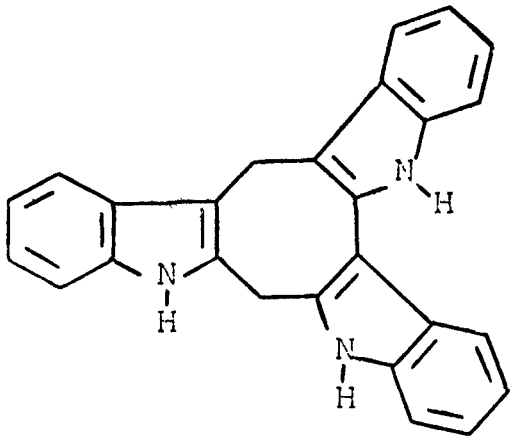


(CLXXXIX)

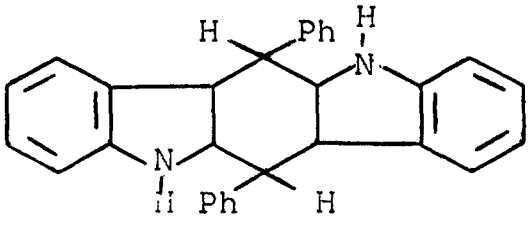


(CXC)

Acid catalysed condensation of 1-methylindole with formaldehyde afforded three indole units fused product (CXCI) whereas dimer (CXCII) was obtained by the reaction of indole and benzaldehyde[107].

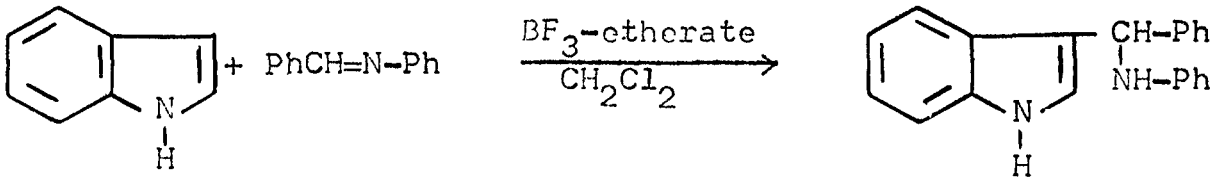


(CXCI)

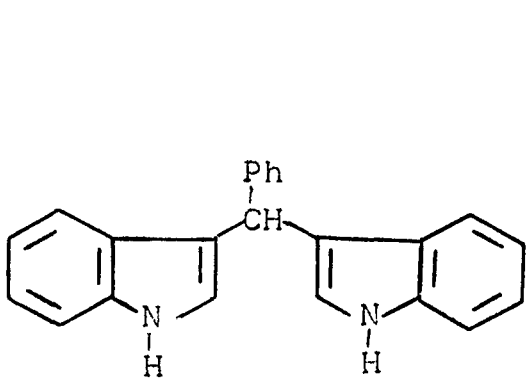


(CXCII)

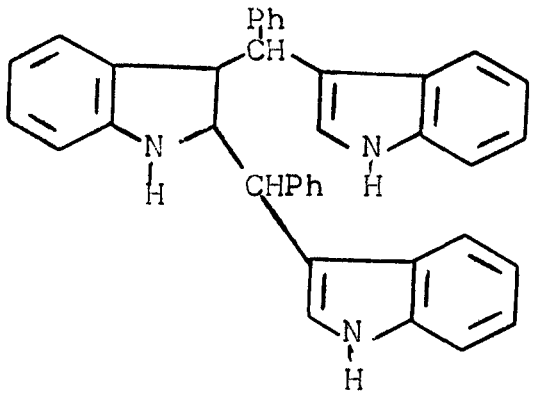
Banerji et al.[108] treated indole with benzalaniline in the presence of BF_3-etherate and obtained an interesting heterocycle (CXCV) presumably formed by the trimeric association of indole through methine units possibly via compounds (CXCIII) and (CXCIV).



(CLXVII) (CXCIII)

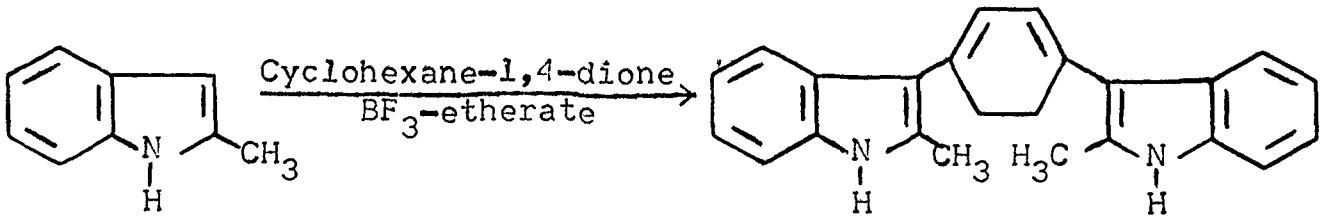


(CXCIV)



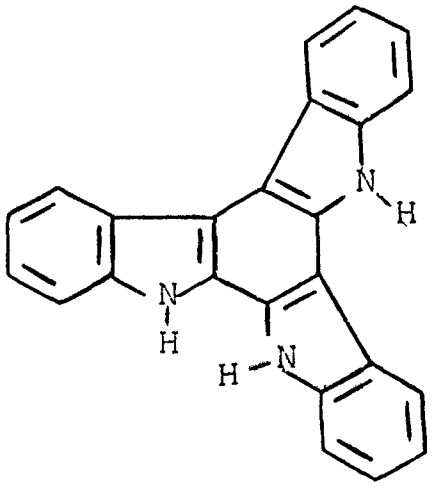
(CXCV)

2-Methylindole on reaction with cyclohexan-1,4-dione in the presence of BF_3-etherate resulted in the isolation of 1,4-bis(2-methylindolyl-3)cyclohexano- $\Delta^{1,3}$-diene[109] (CXCVII).

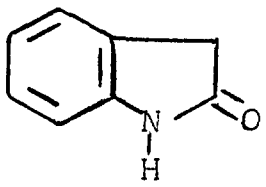


(CXCVI) *(CXCVII)*

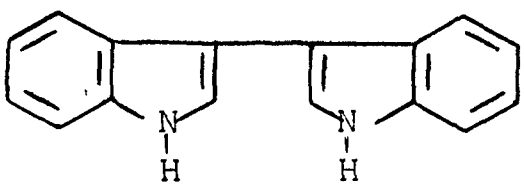
Kaneko et al.[110,111] prepared indole trimer[112] (CXCVIII) by the reaction of indole (CLXVII) with $TiCl_3$ in the presence of hydrogen peroxide. The products varied widely depending upon the pH of the reaction solution. Under acidic conditions indole gave rise to oxiindole (CXCIX), 2,3-biindole (CCII) and trimer (CXCVIII). Under neutral conditions. it was converted to oxiindole 3,3'-biindole (CC) and hydroxyindoles.



(CXCVIII)

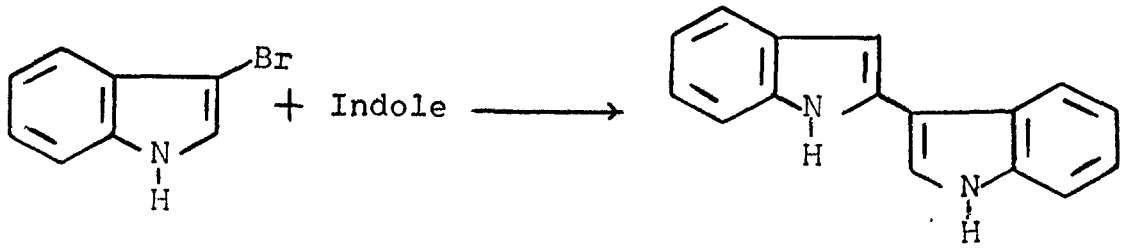


(CXCIX)



(CC)

Bocchi and Palla[113-115] synthesised 3-bromoindoles (CCI) which on reaction with various indoles in the presence of protic or lewis acids provided 2,3'-dimers[116,117] (CCII) in good yields.

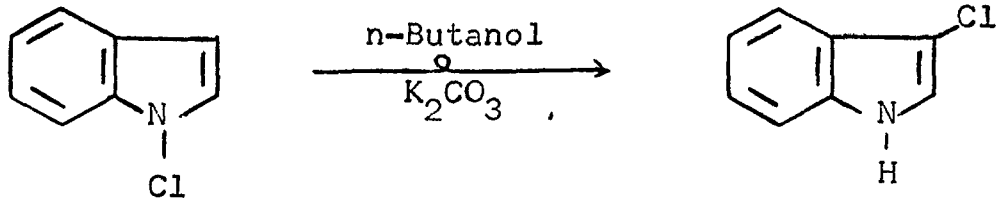


(CCI) (CCII)

The reaction of indoline-2-one or 4,6-dimethoxyindoline-2-one with various substituted indoles in the presence of phosphoryl chloride afforded 2,2', 2,3' and 2,7'-biindolyls[118]. 2,2'-Biindolyls have been synthesised by coupling 2-haloindoles in presence of copper[119]. 2-Alkoxy-3-hydroxyindolines in the presence of lewis acids afforded the same[120].

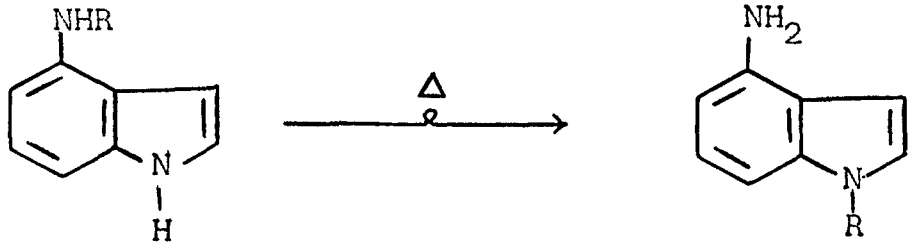
Rearrangements in indole derivatives

De Rosa[121-123] treated indole with sodium hypochlorite to give N-chloroindole (CCIII) which rearranged to give 3-chloro-indole (CCIV) in n-butyl alcohol containing K_2CO_3 under reflux[120].



(CCIII) (CCIV)

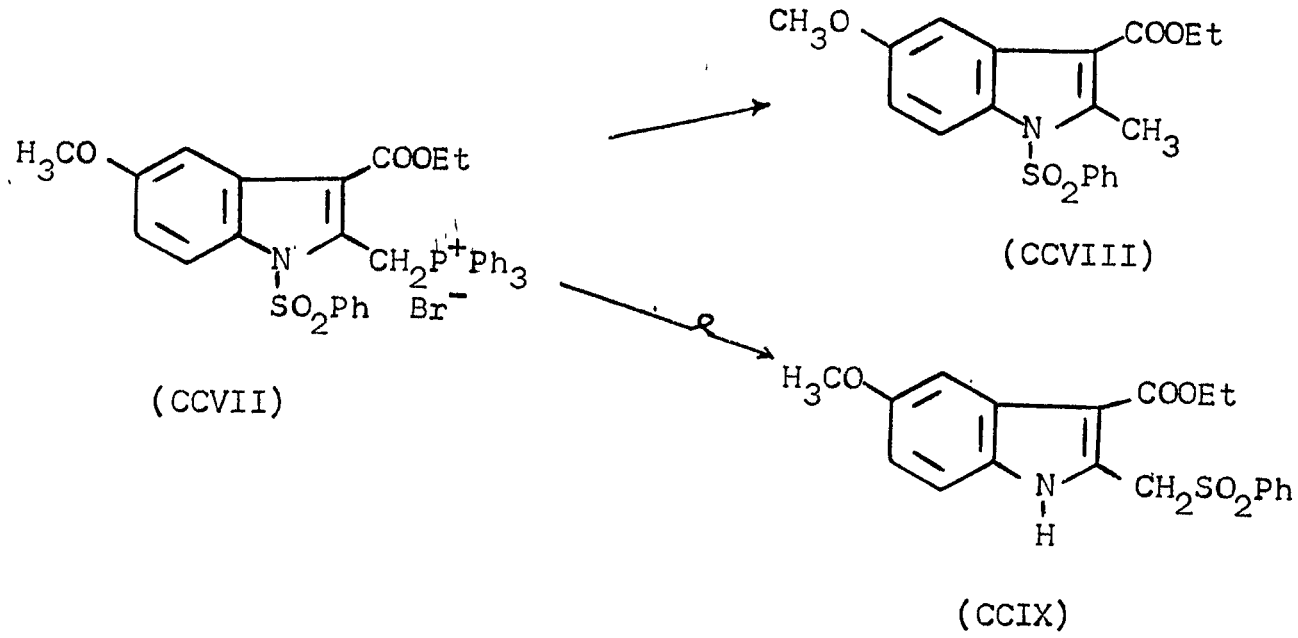
4-Alkylaminoindoles (CCVa-c) rearranged in good yields to the corresponding 1-alkyl-4-aminoindoles (CCVIa-c) in the presence of hydrated toluene-p-sulphonic acid in boiling toluene[124].



(CCV) (CCVI)

R= (a) $-CH_3$, (b) $-CH_2Ph$, (c) $-CH_2-CO_2Et$.

Nagrath nam and Srinivasan[125] reported a novel migration of N-benzene sulphonyl group. The reaction of (CCVII) with NaOH in benzene followed by aq. work up, afforded (CCVIII) and rearranged product (CCIX).



(CCVII)

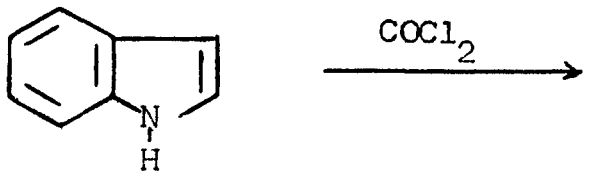
(CCVIII)

(CCIX)

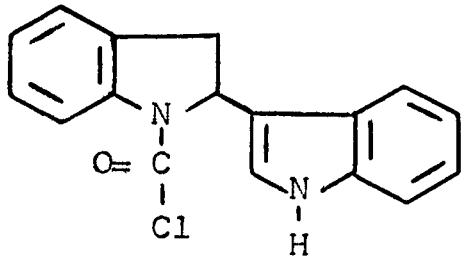
Discussion

The synthesis of 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride was carried out through the reaction of indole with phosgene below 20°.[1] This dimer (CCX) was transformed into the derivatives (CCXI-CCXXI) through its reaction with the appropriate reagents. Synthesis of these dimers was our prime motive, because such compounds have been shown to possess various significant biological properties.

Bergman et al.[102] reported the reaction of 3-methyl-indole with $COCl_2$ yielding product (CLXXX), isolated as the N,N-dimethylamide derivative (CLXXXI). In the present study, a similar treatment of indole (CLXVII) and its dimer (CLXVIII) with phosgene, however, has produced 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (CCX), which is marked by the attachment of COCl group at the nitrogen of indoline moiety only — the indole moiety remains unaffected. This on treatment with suitable reagents furnished a variety of 1-substituted 2,3-dihydro-2,3'-biindoles (CCXI-CCXXI). Thus, the transformation of compound (CCX) into various products constitutes a facile method for obtaining biindoles with a suitable substituent at the nitrogen of indoline moiety.

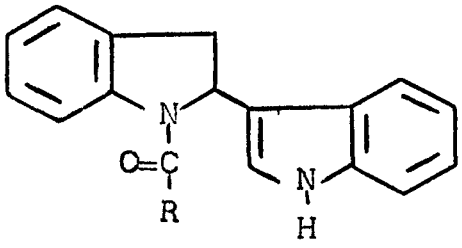


(CLXVII)



(CCX)

RH

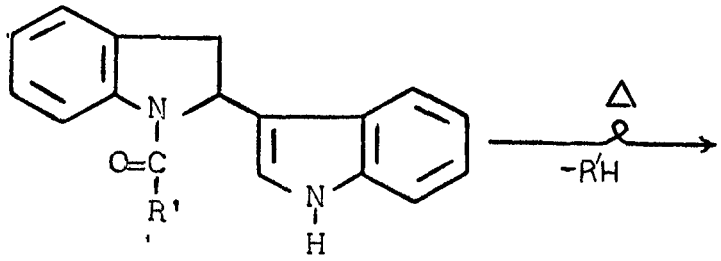


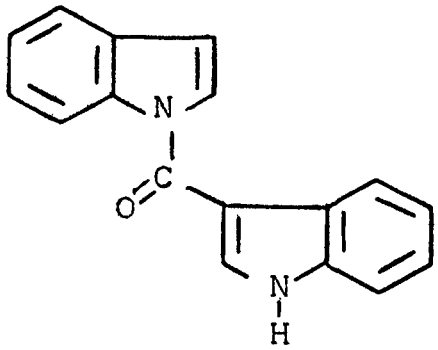
(CCXI-CCXXI)

	R
(CCXI)	$-OCH_3$
(CCXII)	$-OC_2H_5$
(CCXIII)	$-NHCH_3$
(CCXIV)	$-N(CH_3)_2$
(CCXV)	$-NHC_2H_5$
(CCXVI)	$-N(C_2H_5)_2$
(CCXVII)	$-NHCH_2-Ph$
(CCXVIII)	-NHPh
(CCXIX)	$-NH_2$
(CCXX)	$-NHNH_2$
(CCXXI)	-CN

A further study of the driving force that makes the compound (CCX) to change slowly at the room temperature into a more stable product (CLXXIII)[102] involving a novel type of rearrangement, has been discussed. This rearrangement has been

successfully effected on the amino derivatives (CCXIII-CCXVII) of the *compound* (CCX). *Other derivatives did provide the rearranged* product (CLXXIII) but in very low yields.



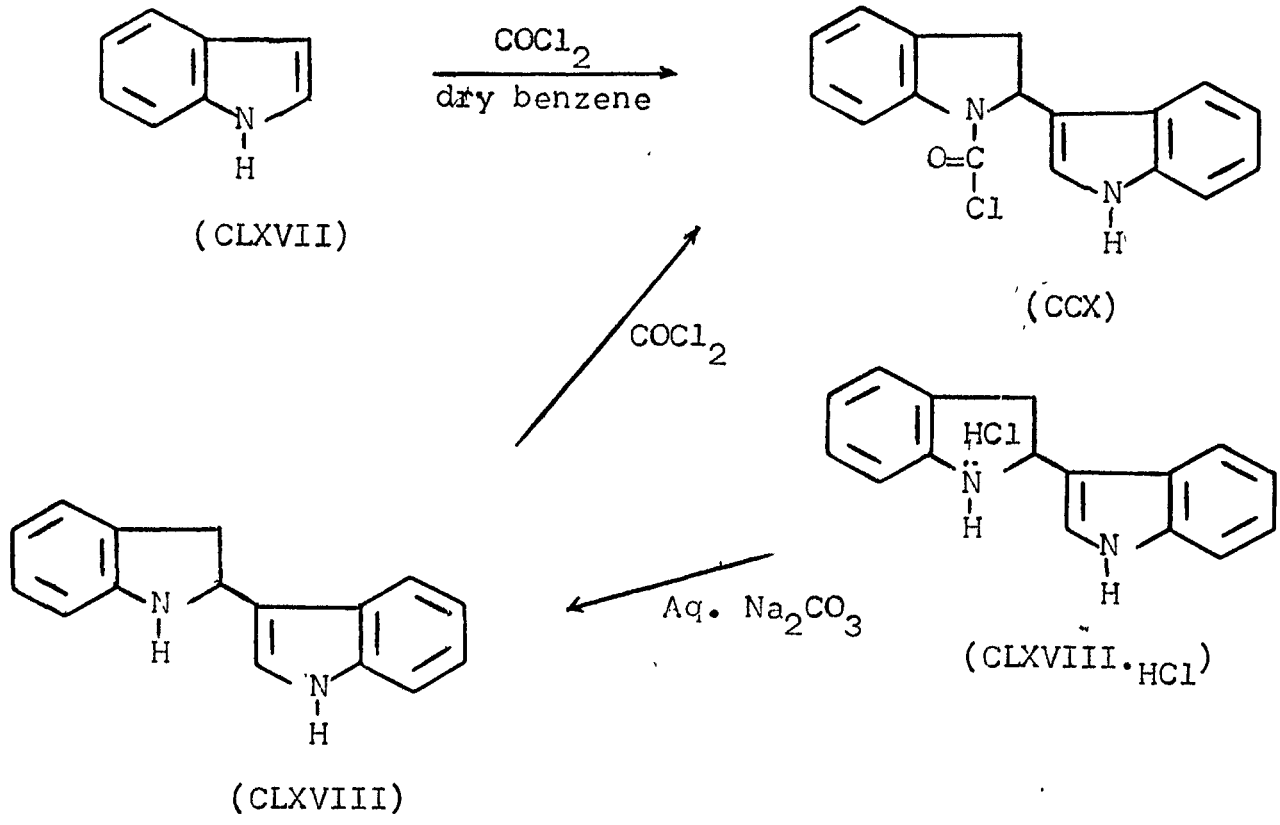


(CLXXIII)

	R'
(CCX)	-Cl
(CCXIII)	$-NHCH_3$
(CCXIV)	$-N(CH_3)_2$
(CCXV)	$-NHCH_2CH_3$
(CCXVI)	$-N(CH_2CH_3)_2$
(CCXVII)	$-NHCH_2-Ph$

Reaction of indole with phosgene

The reaction of indole (CLXVII) with an excess of phosgene below 20° afforded two compounds which melted at 107° and 132° respectively [The former product is obtained from its hydrochloride salt ($CLXVIII._{HCl}$, m.p.150°) by treating with 20% aqueous solution of sodium carbonate].



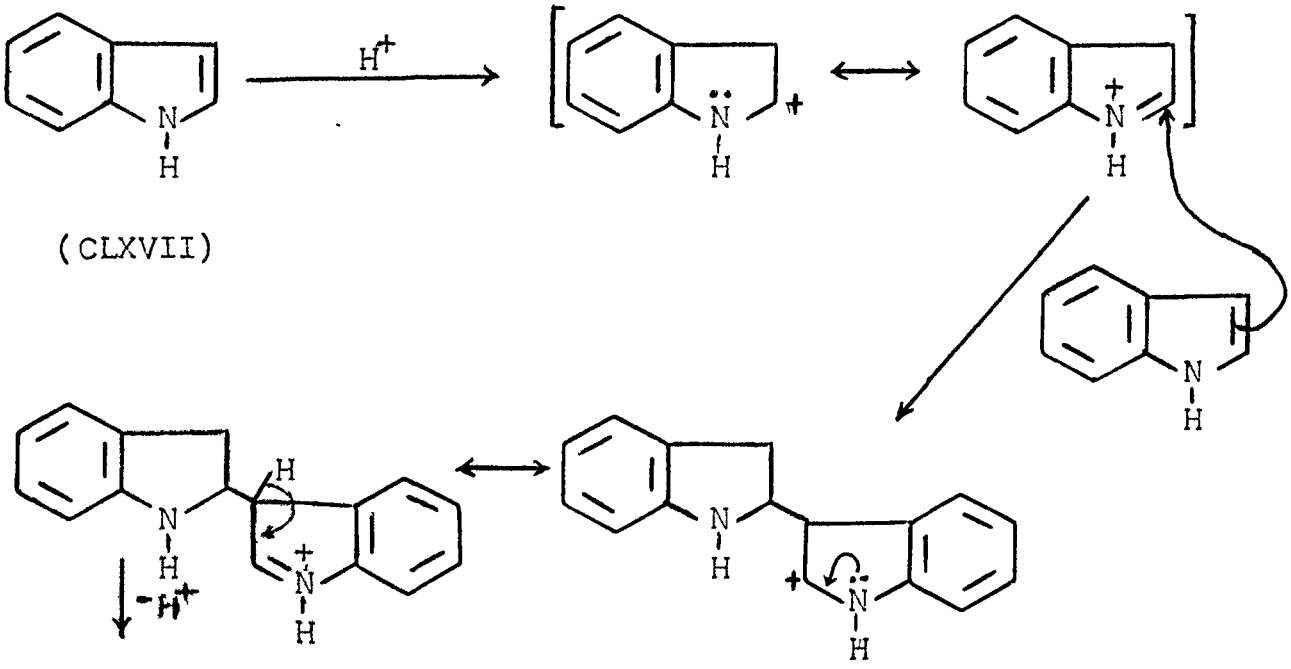
Characterization of the compound, m.p.107° as indole dimer (CLXVIII)

The compound, m.p.107° (reported[99], m.p.108°) exhibited in its IR spectrum, bands at 3220 (C=C-NH), 3185 (CH_2-CH-NH), 1620 (C=C) and 740 cm^{-1} (δC-H, $_{arom.}$). PMR spectrum exhibited a doublet of doublet (J_1=18 Hz, J_2=8 Hz) at δ 3.00 for 2 protons present at C3 of indoline moiety. A triplet at δ 5.20 with J=8 Hz integrating for 1 proton is ascribable to C2-proton adjacent to nitrogen in the same ring. A broad singlet at δ 3.85 (exchangeable with D_2O) was seen due to the NH proton of indoline

moiety. A multiplet centred at δ 7.10 was for 9 protons (8 aromatic + 1 vinylic). A broad doublet like signal at δ 7.50 for 1H (exchangeable with D_2O) is ascribable to the NH proton of the indole ring.

The formation of this dimer from indole has been rationalized in the light of mechanism proposed by Hodson and Smith[98].

Position-3 of indole being the richest in the electron density is most likely to be attacked by an electrophile and consequently the formation of carbonium ion at position-2- which is stabilized by resonance, would simultaneously be attacked by a second molecule of indole resulting in the formation of indole dimer (CLXVIII).



(CLXVII)

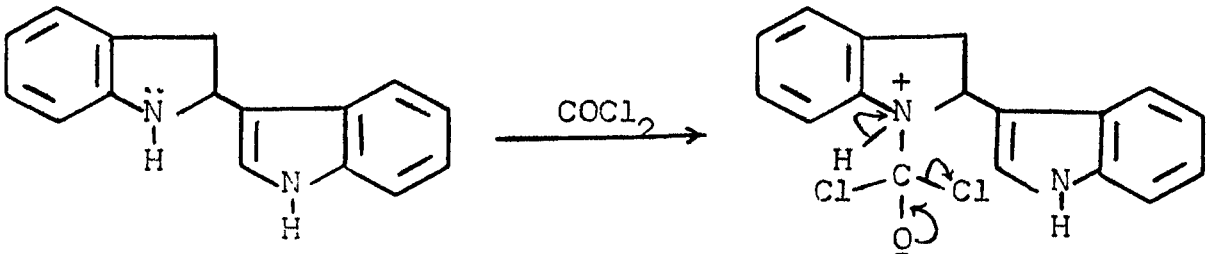
(CLXVIII)

Characterization of the compound, m.p. 132° as 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (CCX)

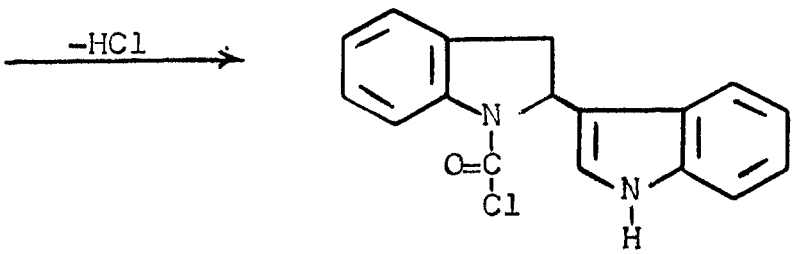
The compound, m.p. 132°, analysing for $C_{17}H_{13}N_2OCl$ showed a positive Beilstein test for halogen. Its mass spectrum giving molecular ion peak at m/z 296 and 298 (3:1) also suggested the presence of chlorine in a dimeric compound as (CCX). The fragment m/z 233 clearly indicated the presence of carbonyl chloride moiety in the product. This was further supported by IR spectrum exhibiting absorption bands at 3320, 1690 and 820 cm^{-1} due to NH, N-COCl, C-Cl stretching frequencies (∂C-H, arom. also merged into C-Cl stretching). The PMR spectrum[105,126] was in agreement with the assigned structure as 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (CCX). It displayed an uneven doublet of a doublet (J_1=17 Hz, J_2=2.5 Hz) at ∂ 3.15 integrating for one proton ascribable to C3-H. Another one-proton doublet of a doublet (J_1=17 Hz, J_2=9 Hz) appearing at ∂ 3.85 could be assigned to the other C_3-proton. One more doublet of a doublet (J_1=9 Hz, J_2=2.5 Hz) integrating for 1H and appearing at ∂ 5.95 was unmistakably[127] attributed to the proton on the carbon atom bearing amide and C=C groups (C2-H of indoline moiety). A multiplet centred at ∂ 7.20 was assigned to aromatic (7H) and vinylic (1H) protons. A one-proton doublet like signal characteristic[128] of the aromatic proton in close proximity to C=O was observed at ∂ 8.00 and attributed to the C7-H of indoline moiety. A broad signal (1H, exchangeable with D_2O) seen at ∂ 10.03 was due to NH proton of indole moiety.

On the basis of the above spectral data, compound having m.p. 132° was assigned the structure of 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (CCX). The confirmation of this structure came from the reaction of indole dimer (CLXVIII) (obtained from dimer hydrochloride)[99] with phosgene, furnishing exclusively a product identical (m.p., m.m.p. and co-TLC) with (CCX).

The mechanism for the formation of product (CCX) on reaction of indole or its dimer with phosgene has been outlined below:



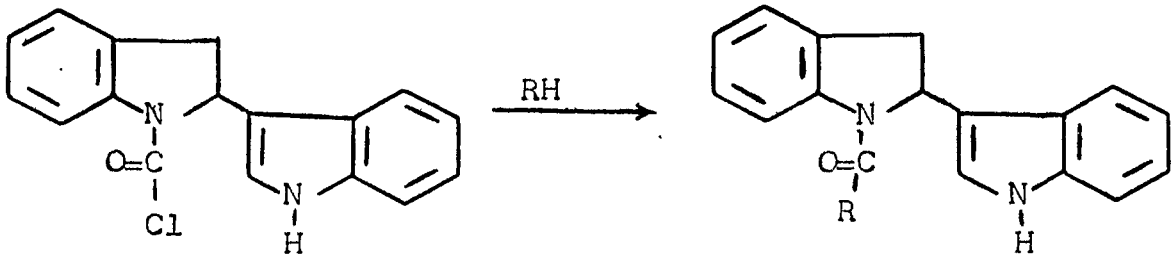
(CLXVIII)



(CCX)

The remarkable feature in the reaction of indole and phosgene is that the -COCl attached at the nitrogen of indoline moiety only— the indole moiety remains unaffected. This is perhaps, due to the electron pair at the nitrogen of the indoline ring being relatively more available to combine with an electron deficient species.

The presence of -COCl moiety in the product has been further supported by its smooth conversion to various derivatives (CCXI-CCXXI). The characterization data for these products have been given in Table-1. (Pages 124-129)



(CCX) (CCXI-CCXXI)

Table - 1

Compound	IR(KBr) cm^{-1}	PMR($CDCl_3$+DMSO-d_6) δ ppm
(CCXI) [R= $-OCH_3$]	3300 (NH), 3080, 3020 (=C-H), 1675 (N-C(=O)-OCH_3), 1590, 1540 ($C=C_{arom.}$), 1120, 1050 (C-O), 750 ($\partial C-H_{arom.}$).	3.15 (dd, J_1=17 Hz; J_2=2.5 Hz, 1H); 3.75 (dd, J_1=17 Hz, J_2=9 Hz, 1H):(C3-protons), 3.67 (s, 3H, -C(=O)-OCH_3), 5.80 (dd, J_1=9 Hz; J_2=2.5 Hz, 1H, C2-H), 7.28 (m, 8H, 7 aromatic + 1 vinylic protons), 7.55 (d, 1H, C7-H), 10.07 (br,s, 1H, exchangeable with D_2O, NH-indole ring).
(CCXII) [R= $-OC_2H_5$]	3290 (NH), 3068, 3015 (=C-H), 1670 (N-C(=O)-OC_2H_5), 1560, 1520 ($C=C_{arom.}$), 740 ($\partial C-H_{arom.}$).	1.17 (t, 3H, N-C(=O)-OCH_2-CH_3), 3.07 (dd, J_1=16 Hz; J_2=3 Hz, 1H); 3.70 (dd, J_1=16 Hz, J_2=10 Hz, 1H): (C3-protons), 4.13 (q, 2H, N-C(=O)-OCH_2-CH_3), 5.77 (dd, J_1=10 Hz; J_2=3 Hz, 1H, C2-H), 7.08 (m, 8H, 7 aromatic + 1 vinylic protons), 7.83 (d-like, 1H, C7-H), 8.83 (br,s, exchangeable with D_2O, NH-indole ring).

Compound	IR(KBr) cm^{-1}	PMR($CDCl_3$+DMSO-d_6) ∂ ppm
(CCXIII) [R= $-NH-CH_3$]	3420 (NH), 3300 (NH-indole ring), 3050, 3030 (=C-H), 1650 (N-C(=O)-N-), 1580, 1520 ($C=C_{arom.}$), 1350 (C-N), 760 ($\partial C-H_{arom.}$).	2.67 (s, 3H, N-C(=O)-N-CH_3), 3.06 (dd, J_1=17 Hz; J_2=3 Hz, 1H), 3.78 (dd, J_1=17 Hz; J_2=10 Hz, 1H): (C3-protons), 5.50 (dd, J_1=10 Hz; J_2=3 Hz, 1H, C2-H), 7.20 (m, 8H, 7 aromatic + 1 vinylic protons), 8.06 (d, 1H, C7-H), 9.51 (br,s, exchangeable with D_2O, NH-indole ring).
(CCXIV) [R= $-N(CH_3)_2$]	3280 (NH-indole ring), 3040, 3010 (=C-H), 1650 (N-C(=O)-N-), 1570, 1550 ($C=C_{arom.}$), 1360 (C-N), 750 ($\partial C-H_{arom.}$).	2.90 (s, 6H, N-C(=O)-N-CH_3), 3.50 (dist. d, J_1=10 Hz, 2H, C3-protons), 5.72 (t, J=10 Hz, 1H, C2-H), 7.17 (m, 9H, 7 aromatic + 1 vinylic protons), 7.75 (d-like, 1H, C7-H), 9.50 (1H, exchangeable with D_2O, NH-indole ring).

Compound	IR(KBr) cm^{-1}	PMR($CDCl_3$+DMSO-d_6) δ ppm
(CCXV) [R= $-NH-CH_2-CH_3$]	3475 (NH), 3280 (NH-indole ring), 1648 (N-C(=O)-N-), 1570, 1530 ($C=C_{arom.}$), 1358 (C-N), 765 ($\partial C-H_{arom.}$).	1.12 (t, 3H, $-N-C(=O)-NH-CH_2-CH_3$), 3.10 (dd, J_1=15.5 Hz; J_2=3 Hz, 1H); 3.68 (dd, J_1=15.5 Hz; J_2=9 Hz, 1H):(C3-protons), 3.98 (q, 2H, $-NH-CH_2-CH_3$), 5.73 (dd, J_1=9 Hz, J_2=3 Hz, 1H, C2-H), 7.13 (m, 8H, 7 aromatic + 1 vinylic protons), 7.90 (dist. d, 1H, C7-H), 9.23 (br,s, 1H, exchangeable with D_2O, NH-indole ring).
(CCXVI) [R= $-N(C_2H_5)_2$]	3310 (NH-indole ring), 1652 (-N-C(=O)-N-), 1558, 1510 ($C=C_{arom.}$), 1358 (C-N), 748 ($\partial C-H_{arom.}$).	1.15 (t, 6H, $CH_3-CH_2-N-CH_2-CH_3$), 2.85 (q, 4H, $CH_3-CH_2-N-CH_2-CH_3$), 3.04 (dist. d, J=10 Hz, 2H, C3-protons), 5.70 (t-like, J=10 Hz, 1H, C2-H), 7.20 (m, 8H, 7 aromatic + 1 vinylic protons), 7.72 (d, 1H, C7-H), 9.30 (br,s, 1H, exchangeable with D_2O, NH-indole ring).

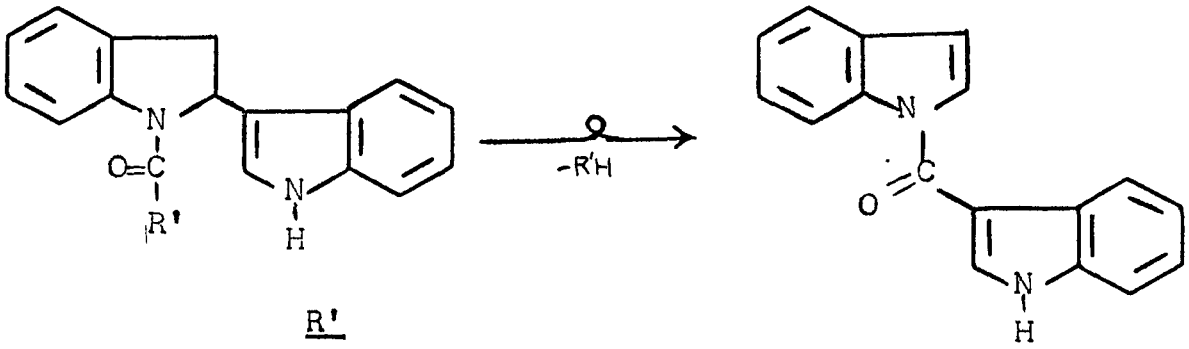
Compound	IR(KBr) cm^{-1}	PMR($CDCl_3$+DMSO-d_6) δ ppm
(CCXVII) [R= -NH-CH_2-Ph]	3410 (NH-CH_2-Ph), 3286 (NH-indole ring), 3084, 3028 (=C-H), 1656 (N-C(=O)-N), 1580, 1540 ($C=C_{arom.}$), 1350 (C-N), 748 ($\partial C-H_{arom.}$).	3.08 (dd, J_1=16.8 Hz; J_2=2.5 Hz, 1H); 3.82 (dd, J_1=16.8 Hz; J_2=9 Hz, 1H):(C3-protons), 4.85 (s, 2H, -CH_2-Ph), 5.80 (dd, J_1=9 Hz, J_2=2.5 Hz, 1H, C2-H), 7.35 (m, 14H, 13 aromatic + 1 vinylic protons), 7.95 (d, 1H, C7-H), 10.02 (br,s, 1H, exchangeable with D_2O, NH-indole ring).
(CCXVIII) [R= -NH-Ph]	3360, 3325 (NH-Ph, NH-indole ring), 3050, 3038 (C=C-H), 1638 (N-C(=O)-NH-Ph), 1590, 1530 ($C=C_{arom.}$), 740 ($\partial C-H_{arom.}$).	3.12 (dd, J_1=16.5 Hz; J_2=2.5 Hz, 1H); 3.78 (dd, J_1=16.5 Hz; J_2=9 Hz, 1H):(C3-protons), 5.98 (dd, J_1=9 Hz; J_2=2.5 Hz, 1H, C2-H), 7.4 (m, 14H, 13 aromatic + 1 vinylic protons), 8.86 (br,s, 1H, exchangeable with D_2O, -NH-indole ring).

Compound	IR(KBr) cm^{-1}	PMR($CDCl_3$+DMSO-d_6) δ ppm
(CCXIX) [R= $-NH_2$]	3480, 3320 ($-NH_2$), 3280 (NH-indole ring), 1650 (N-C(=O)-N), 1580, 1530 ($C=C_{arom.}$), 1364 (C-N), 770 ($\partial C-H_{arom.}$).	3.10 (dd, J_1=15 Hz; J_2=3 Hz, 1H); 3.71 (dd, J_1=15 Hz; J_2=10 Hz, 1H):(C3-protons), 3.20 (br,s, 2H, N-C(=O)-NH_2, exchangeable with D_2O), 5.65 (dd, J_1=10 Hz; J_2=3 Hz, 1H, C2-H), 7.08 (m, 8H, 7 aromatic + 1 vinylic protons), 8.00 (d, 1H, C7-H), 9.5 (br,s, 1H, exchangeable with D_2O, NH-indole ring).
(CCXX) [R= $-NH-NH_2$]	3420-3340 ($NH-NH_2$), 3260 (NH-indole ring), 3060, 3030 (=C-H), 1575, 1525 ($C=C_{arom.}$), 1645 (N-C(=O)-NH_2), 760 ($\partial C-H_{arom.}$)	3.10 (dd, J_1=16 Hz; J_2=3 Hz, 1H); 3.73 (dd, J_1=16 Hz, J_2=9.5 Hz, 1H):(C3-protons), 3.40 (m, 3H, $-NH-NH_2$, disappeared on ahaking with D_2O), 5.75 (dd, J_1=9.5 Hz, J_2=3 Hz, 1H, C2-H), 7.05 (m, 8H, 7 aromatic + 1 vinylic protons), 8.00 (dist. d, 1H, C7-H), 10.83 (br,s, 1H, exchangeable with D_2O, NH-indole ring).

Compound	IR(KBr) cm^{-1}	PMR($CDCl_3$+DMSO-d_6) ∂ ppm
(CCXXI) [R= -CN]	3320 (NH-indole ring), 3080, 3050 (=C-H), 2230 (weak, C≡N), 1680 (N-C(=O)-CN), 1560, 1510 ($C=C_{arom.}$), 740 ($\partial C-H_{arom.}$).	3.20 (dd, J_1=17 Hz; J_2=3 Hz, 1H), 3.81 (dd, J_1=17 Hz; J_2=8.5 Hz, 1H):(C3-protons), 6.03 (dd, J_1=8.5 Hz; J_2=3 Hz, 1H, C2-H), 7.16 (m, 8 H, 7 aromatic +1vinylic protons), 8.13 (d-like, 1H, C7-H), 9.80 (br,s, 1H, exchangeable with D_2O, NH-indole ring).

Thermal rearrangement of 2,3-dihydro[2,3'-biindole]-1-carbonyl chloride (CCX) and its amino derivatives (CCXIII-CCXVII): Formation of 1,3'-carbonyl biindole (CLXXIII)

The partial change of compound (CCX) even at room temperature motivated a study of the driving force that initiates this transformation. The substrate (CCX) and its amino derivatives (CCXIII-CCXVII) on direct heating or in the presence of a solvent were smoothly converted in high yields into a product identified as 1,3'-carbonyl biindole (CLXXIII) by comparison (m.p. and spectral properties) with an authentic specimen. Other derivatives also provided the rearranged product (CLXXIII) but in very low yields.

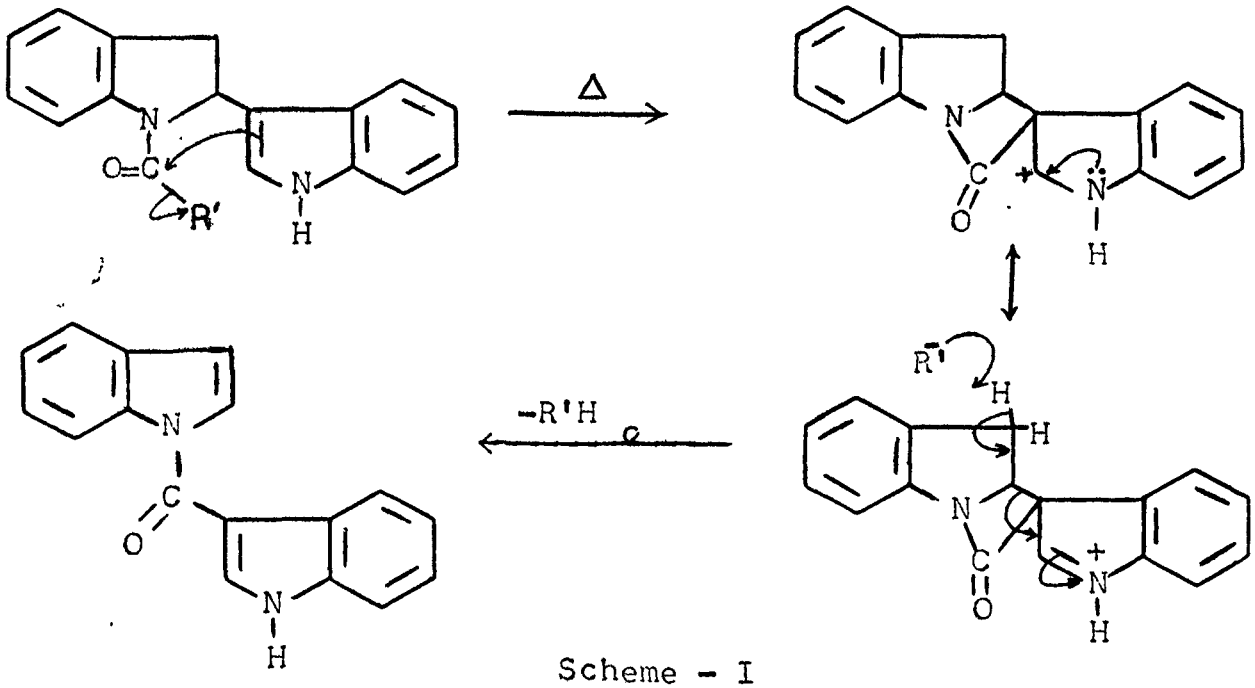


	R'
(CCX)	-Cl
(CCXIII)	$-NHCH_3$
(CCXIV)	$-N(CH_3)_2$
(CCXV)	$-NHCH_2CH_3$
(CCXVI)	$-N(CH_2CH_3)_2$
(CCXVII)	$-NHCH_2-Ph$

(CLXXIII)

The product (CLXXIII), m.p.226° (reported[102], m.p.227°) showed a molecular ion peak at m/z 260 and a base peak at m/z 117 in its mass psectrum. The IR spectrum showed absorption bands at 3320 and 1650 cm^{-1} compatible with -NH and -N-CO-C=C- stretching frequencies respectively. Its PMR spectrum showed a multiplet centred at δ 7.30 for 10 protons (7 aromatic + 3 vinylic) and a doublet alike signal for one proton (C7-H) in close proximity to C=O. A broad signal for one proton at δ 10.7 (exchangeable with D_2O) indicated the presence of only one NH proton, thus showingthat the carbonyl group is linked to one of the nitrogen atoms.

An interesting feature in the formation of the product (CLXXIII) is the migration of the indole system to the carbonyl group, followed by deprotonation. A probable mechanism for the transformation (CCX, CCXIII-CCXVII) ⟶ (CLXXIII) is outlined in the schemeI.



Scheme - I

The attack of the electrophilic centre by the relatively electron rich C3' of the indole ring leads to a carbonium ion at C2' which is further resonance stabilized by the lone pair of the adjacent nitrogen. Attack at C2' is not so likely as the resultant carbonium ion at C3' would not be as favourable. The greater stability of the resonance stabilized carbonyl group in (CLXXIII), compared to that in the substrates (CCX, CCXIII-CCXVII) provides the driving force necessary for the cleavage of the C-C linkage.

Other products formed in minute quantities were not isolated. However, some of the products formed during the reaction of indole with phosgene[102] can be explained by assuming the substrate (CCX) to be the intermediate.

Experimental

Preparation of indole dimer (CLXVIII)

To a solution of indole (5.0 g) in dry benzene (100 ml) was passed dry hydrogen chloride gas (3.0 g) during a span of 30 min. The dimer hydrochloride, thus precipitated was filtered, washed with dry benzene and air dried. The hydrochloride salt of the dimer (CLXVIII.$_{HCl}$ m.p.150°, reported[99], m.p.150°) was shaken with 25% sodium carbonate solution and extracted with ether. The ethereal solution containing the dimer was dried over anhyd. sodium sulphate and filtered. Removal of the solvent on a steam bath provided 2,3-dihydro-2,3'-biindole (CLXVIII), which was crystallized from petrol-ether mixture (7:3). Yield, 4.0 g; m.p.107° (reported[99], m.p.108).

IR(KBr) : ν_{max} 3220 (=C-NH), 3185 (-CH-NH), 1620 (C=C) and 740 cm^{-1} ($\delta C-H_{arom.}$).

PMR($CDCl_3$) : δ 3.00 (dd, $J_1 \approx 18$ Hz, $J_2 = 8$ Hz, 2H, C3-protons of indoline moiety), 3.85 (s, 1H, exchangeable with D_2O, N<u>H</u>-indoline moiety), 5.20 (t, J=8 Hz, 1H, C2-<u>H</u> of indoline moiety), 7.10 (m, 9H, 8 aromatic + 1 vinylic), 7.50 (d, 1H, exchangeable with D_2O, N<u>H</u>-indole ring).

Reaction of indole with phosgene: 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (CCX)

A solution of indole (3.0 g) in benzene (75 ml) was treated with phosgene gas (5.0) in 30 min. duration with occasional shaking at a temperature below 20° (progress of the reaction was monitored by TLC). After the reaction was over (2 hr), the precipitated dimer hydrochloride was filtered off in a fuming chamber and the filtrate evaporated under reduced pressure by passing the vapours through 20% KOH solution or by exposing the filtrate to air in a fuming chamber (heating of the filtrate was avoided in order to get a single product). A crystalline material separated during the evaporation, was filtered on a buckner funnel and recrystallized from ethyl acetate-benzene (1:3). Yield, 1.8 g; m.p. 132°.

MS : m/z 296, 298 (M^+, 7.5, 2.5%), 261 (M^+-Cl, 90.4%), 260 (M^+-HCl, 100%, base peak), 233 (M^+-COCl, 9.14%), 117 ($C_3H_7N^+$, 19.23%).

IR(KBr) : ν_{max} 3320 (NH), 3080, 3020 (=C-H), 1690 (N-COCl), 1590, 1540 ($C=C_{arom.}$), 820 (C-Cl) and 740 cm^{-1} ($\partial C-H_{arom.}$).

PMR($CDCl_3$+ DMSO-d_6) : δ 3.15 (dd, J_1=17 Hz; J_2=2.5 Hz, 1H, C3-H), 3.85 (dd, J_1=17 Hz; J_2=9 Hz, 1H, other C3-H), 5.95

(dd, J_1=9 Hz; J_2=2.5 Hz, 1H, C2-H), 7.28 (m, 8H, 7 aromatic + 1 vinylic protons), 7.55 (d, 1H, C7-H), 10.07 (br,s, 1H, exchangeable with D_2O, NH-indoline ring).

Analysis Found : C, 69.41; H, 4.32; N, 9.39;

$C_{17}H_{13}N_2OCl$ requires : C, 69.47; H, 4.38; N, 9.44%.

Reaction of indole dimer (CLXVIII) with phosgene: 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (CCX)

A solution of indole dimer (2.0 g) in dry benzene (50 ml) was treated with phosgene gas (2.0 g) during a span of 20 min. with occasional shaking of the reaction mixture at a temperature below 20° (progress of the reaction was checked through TLC). After the completion of reaction, the solvent was evaporated under reduced pressure or by exposing the filtrate to air in a fuming chamber (heating of the filtrate was avoided in order to get a single product). A crystalline material thus separated was filtered on a buckner funnel and recrystallization from ethyl acetate-benzene (1:3) gave compound (CCX). Yield, 1.3 g; m.p.132°.

Preparation of 1-carbomethoxy-2,3-dihydro-2,3'-biindole (CCXI)

The compound (CCX) (1.0 g) dissolved in methanol (50 ml, 80%) was stirred on a magnetic stirrer at room temperature in the presence of $Ba(OH)_2$ (1.0 g) for a period of 2 hr. (progress of the reaction was checked through TLC). After the reaction was complete, solvent reduced to 10 ml and the contents poured into cold water. It was then extracted with ether and the ethereal layer washed twice with water dried over anhyd. sodium sulphate and the dessicant removed. Removal of the solvent gave an oily residue which on crystallization from methanol gave product (CCXI). Yield, 0.8 g; m.p.173°.

The spectral data (IR and PMR) of the derivatives (CCXI-CCXXI) has been described in the table-1 in discussion (p.124-129).

Analysis Found : C, 73.89; H, 5.39; N, 9.51;

$C_{18}H_{16}N_2O_2$ requires : C, 73.97; H, 5.48; N, 9.59%.

Preparation of 1-carboethoxy-2,3-dihydro-2,3'-biindole (CCXII)

A mixture of (CCX) (1.0 g) and ethyl alcohol (50 ml, 80%) was stirred on a magnetic stirrer at room temperature in the presence of $Ba(OH)_2$ (1.0 g) for a period of 2 hr. After the reaction was complete (TLC), the reaction mixture was worked up in the usual way to get an oil, which was purified on the silica gel

column. Crystallization from ethanol gave the crystalline product (CCXII). Yield, 0.65 g; m.p.136°.

Analysis Found : C, 74.58; H, 6.00; N, 9.10;

$C_{19}H_{18}N_2O_2$ requires : C, 74.51; H, 5.88; N, 9.15%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-N-methylcarboxamide (CCXIII)

A solution of (CCX) (1.0 g) in THF (25 ml) was mixed with methyl amine (5 ml) and kept at room temperature for 2 hr. by which time the reaction was complete. The reaction mixture was poured into water and the compound thus separated was filtered on a buckner funnel. This on crystallization from methanol gave compound (CCXIII). Yield, 0.75 g; m.p.183°.

Analysis Found : C, 74.21; H, 5.91; N, 14.45;

$C_{18}H_{17}N_3O$ requires : C, 74.23; H, 5.84; N, 14.43%.

Preparation of 2,3'-dihydro-[2,3'-biindole]-1-N,N-dimethyl-carboxamide (CCXIV)

Under similar reaction conditions, compound (CCX) (1.0 g) taken in THF (25 ml), when treated with dimethyl amine (5 ml) yielded product (CCXIV) (from methanol). Yield, 0.85 g; m.p.190°.

Analysis Found : C, 74.81; H, 6.19; N, 13.72;

$C_{19}H_{19}N_3O$ requires : C, 74.75; H, 6.23; N, 13.77%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-N-ethylcarboxamide (CCXV)

The compound (CCX) (1.0 g) in THF (25 ml), treated with ethyl amine (5 ml) under similar reaction condition to produce (CCXV), crystallized from methanol. Yield, 0.7 g; m.p.178°.

Analysis Found : C, 74.71; H, 6.29; N, 13.80;

$C_{19}H_{19}N_3O$ requires : C, 74.75; H, 6.23; N, 13.77%.

Preparation of 2,3-dihydro-[2,3'-biindole)-1-N,N-diethylcarboxamide (CCXVI)

The compound (CCX) (1.0 g) dissolved in 25 ml THF, when treated with diethyl amine (10 ml), produced (CCXVI) (from methanol). Yield, 0.6 g; m.p.169°.

Analysis Found : C, 75.63; H, 6.99; N, 12.54;

$C_{21}H_{23}N_3O$ requires : C, 75.68; H, 6.91; N, 12.61%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-N-benzylcarboxamide (CCXVII)

Using similar procedure, the reaction of (CCX) (1.0 g) in THF, 20 ml with benzyl amine (5 ml) afforded on crystallization from methanol a product (CCXVII). Yield, 0.75 g; m.p. 205°.

Analysis Found : C, 78.50; H, 5.65; N, 11.37;

$C_{24}H_{21}N_3O$ requires : C, 78.47; H, 5.72; N, 11.44%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-carboxanilide(CCXVIII)

A solution of the compound (CCX) (1.0 g) in THF (25 ml) mixed with aniline (10 ml) in an identical manner, furnished product (CCXVIII) (from alcohol). Yield, 0.8 g; m.p. 173°.

Analysis Found : C, 78.16; H, 5.45; N, 11.98;

$C_{23}H_{19}N_3O$ requires : C, 78.19; H, 5.38; N, 11.90%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-carboxamide (CCXIX)

The dimer (CCX) (1.0 g) in 30 ml THF when reacted with liquor ammonia (d, 0.91; 10 ml) gave (CCXIX) (crystallized from methanol). Yield, 0.7 g; m.p. 208°.

Analysis Found : C, 73.59; H, 5.50; N, 5.21;

$C_{17}H_{15}N_3O$ requires : C, 73.65; H, 5.42; N, 5.16%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-carboxahydrozamide (CCXX)

Usual treatment of the compound (CCX) (1.0 g) in THF (25 ml) with hydrazine (5 ml) provided compound (CCXX) (methanol). Yield, 0.8 g; m.p.185°.

Analysis Found : C, 69.95; H, 5.41; N, 19.08;

$C_{17}H_{16}N_4O$ requires : C, 69.86; H, 5.48; N, 19.18%.

Preparation of 2,3-dihydro-[2,3'-biindole]-1-carbonylcyanide (CCXXI)

1.0 g of compound (CCX) dissolved in 25 ml of dioxane mixed with an aqueous solution of KCN (10 ml, 50%) was stirred at room temperature for 4 hr. Then the reaction was poured into water and product (CCXXI) collected on buckner funnel, was crystallised from alcohol. Yield, 0.6 g; m.p.163°.

Analysis Found : C, 75.22; H, 4.59; N, 14.70;

$C_{18}H_{13}N_3O$ requires : C, 75.26; H, 4.53; N, 14.63%.

Rearrangement of 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (CCX) and its ammino derivatives (CCXIII-CCXVII): Preparation of 1,3'-carbonyl biindole (CLXXIII)

The starting biindole (CCX, CCXIII-CCXVII) (1.0 g) was heated on a heating mantel until it melted [(CCX)132°; (CCXIII) 183°; (CCXIV) 190°; (CCXV) 178°; (CCXVI) 169°; (CCXVII) 205°]. It was then cooled and heated again to its m.p. This process was repeated for 30 min. at which time the reaction was complete (TLC). The solid was dissolved in ethyl acetate and the solution was washed successively with water, sodium bicarbonate solution (~2%) and excess of water, and dried over anhyd. sodium sulphate. Removal of the solvent gave a solid which was chromatographed on a silica gel column to afford the product (CLXXIII) which was crystallized from methanol. Yield, 0.6 g; m.p. 226° (reported[102], m.p. 227°).

MS : m/z 260 (M^+, 19.7%) and 117 ($C_8H_7N^+$, 100%).

IR(KBr) : ν_{max} 3320 (NH), 3080, 3020 (C=C-H), 1680 (-N-CO-C=C-), 1590 and 1540 cm^{-1} ($C=C_{arom.}$).

PMR($CDCl_3$+ DMSO-d_6) : δ 7.3 (mc, 10H, 7 aromatic + 3 vinylic protons), 7.6 (d, 1H, C7-H), 10.7 (br,s, 1H, exchangeable with D_2O, NH).

The product (CLXXIII) could also be prepared from (CCX) in particular by the following procedures.

(a) A solution of compound (CCX) (1.0 g) in benzene (50 ml) was refluxed on a steam bath for 2 hr. by which time the reaction was complete. Benzene was removed and the residue dissolved in ethyl acetate. This solution was then washed repeatedly with water and dried over anhyd. sodium sulphate. Removal of the solvent provided a solid which was purified on a silica gel column to give (CLXXIII). Yield, 0.5 g.

(b) Compound (CCX) (1.0 g), on treatment with 10% aqueous KOH (50 ml) at reflux temperature for 1 hr followed by usual work up and purification through column chromatography, furnished the product (CLXXIII) in better yield. Yield, 0.7 g.

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LIST OF PUBLICATIONS

Papers included in the Thesis

1. "Synthesis of 2,3-Dihydro-(2,3'-biindole)-1-carbonyl Chloride and its derivatives", Indian J.Chem.23B,(1984)986.
2. "A Novel Thermal Rearrangement of 2,3-Dihydro-2-(indol-3-yl) -1-carbonyl Chloride and its Amino Derivatives", J.Chem. Research(s) (1985)230.
3. "Steroidal Cyanoamines: Catalytic Hydrogenation of Steroidal Nitrocyanides", Indian J.Chem. 24B (1985)626.
4. "Synthesis of 5α-Cyanochloestan-6-ones", Indian J.Chem. 25B (1986)301.
5. "Synthesis of some New Cyano-azasteroids", Indian J.Chem. (communicated).

Other Research Papers

6. "A Novel Method for Preparation of Steroidal Ketoximes from Nitroolefins", Indian J.Chem. 23B (1984)801.
7. "Synthesis of some New Cyanosteroids", Indian J.Chem. (In Press).

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Steroidal Cyanoamines: Catalytic Hydrogenation of Steroidal Nitrocyanides

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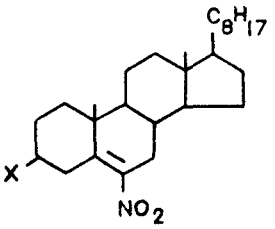
Steroidal nitrocyanides (V-VIII), prepared from nitroolefins (I-IV), on hydrogenation using Raney-nickel as catalyst afford the hitherto unreported steroidal cyanoamines (X) and (XI) in excellent yields. These products have been characterized on the basis of elemental analyses and spectral data.

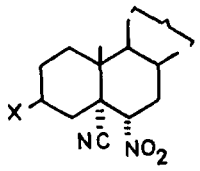
The required nitrocyanides (V-VIII) were obtained in ~90% yield (except in the case of substrate II which gave a mixture of V and VI) by treating the nitroolefins (I-IV) with KCN[1], and characterized on the basis of their elemental analyses and spectral data (Table 1) The IR spectra of these compounds exhibited absorption bands due to C≡N (2240-2250 cm^{-1}) and NO_2 (1560-1570 and 1370-1390 cm^{-1}) functions. The structures assigned were further substantiated by the PMR spectra wherein the α-orientation of cyano group at C-5 was attributed to the half-band width ($W_{1/2}$ = 17-19 Hz; A/B *trans*) for C_3-proton (axial) appearing as a multiplet in 3β-substituted products (V, VI and VIII). The *trans*-orientation of A and B rings in VII[1] was also assigned in a similar manner. A multiplet ($W_{1/2}$ = 17-19 Hz) (three peaks resolved in all the cases) at δ 4.5-4.8 for one proton indicated the C_6-proton to be axial. Had this proton[2] bean equatorial (α-oriented), it could have been observed as a narrow triplet with $J \simeq 3$ Hz. Moreover, the α-nitro (equatorially oriented) at C-6 is preferred over its β-analogue because in the latter case, 1,3-diaxial interaction between C_{10}-methyl and C_6-β-nitro would be unfavourable.

5-Cyano-3β-hydroxy-6α-nitro-5α-cholestane (V) was treated with Jone's reagent to get its 3-oxo derivative (IX) which can be used in further synthetic work.

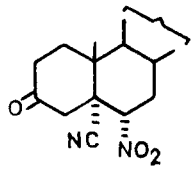
The hydrogenation of V in the presence of Raney-nickel (which has been shown to be a good catalyst for the conversion of a nitro group into an amine)[3] at 30 psi provided a compound (m.p. 185°) which analysed for $C_{28}H_{48}N_2O$ indicating the formation of a cyanoamine. Its IR spectrum displayed absorption bands at 3410 and 3350, 3300 cm^{-1} due to OH and NH_2 functions respectively. A band at 2235 cm^{-1} was observed for C≡N stretching. The absence of a band in the region 1550-1570 cm^{-1} supported the selective reduction of nitro group into an amine; the CN group remained unaffected[4]. Bands at 1620 and 900 cm^{-1} were compatible with N−H bending vibrations. The PMR spectrum of this compound exhibiting a multiplet at δ 4.0 ($W_{1/2}$ = 19 Hz) for one proton (C3-αH) suggested *trans*-orientation of A and B rings. A broad signal for one proton at δ 3.4 which disappeared on shaking with D_2O was ascribable to C_3-OH proton. Another one-proton multiplet ($W_{1/2}$ = 24 Hz) centred at δ 2.80 was assigned to the C_6-βH. The amino group protons were buried into the methylene envelope. These data led to the formation of the product as 6α-amino-5-cyano-3β-hydroxy-5α-cholestane (X).



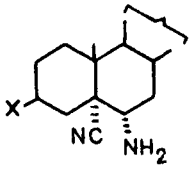
	X
(I)	OH
(II)	OAc
(III)	H
(IV)	Cl



	X
(V)	OH
(VI)	OAc
(VII)	H
(VIII)	Cl



(IX)



	X
(X)	OH
(XI)	H

Under similar conditions, hydrogenation of 3β-acetoxy-5-cyano-6α-nitro-5-α-cholestane (VI) afforded a compound (m.p. 185°), identical (m.p., m.m.p., co-TLC and IR) with that obtained from V. This indicates that hydrogenation of VI also brings about conversion of C_3-acetate into C_3-OH.

Hydrogenation of 5-cyano-6α-nitro-5α-cholestane (VII) gave a product (m.p. 120°) which analysed for $C_{28}H_{48}N_2$ indicating the conversion of nitro group into amino group. The IR spectrum of this product displaying absorption bands at 3395, 3350 (NH_2), 2240 (C≡N) and 1600, 880 cm^{-1} (NH-bending) also supported the above contention. The structure XI assigned to this product was supported by PMR spectrum which exhibited a multiplet ($W_{1/2}$ = 22 Hz) for one proton centred at δ 2.75. This half-band width clearly shows α-orientation for the amino group at C-6. NH_2 protons were found to be merged with the methylene protons.

Hydrogenation of 3β-chloro-5-cyano-6α-nitro-5α-cholestane (VIII) in a similar way furnished a product (m.p. 120°) which gave a negative Beilstein test indicating dechlorination during reduction; such a phenomenon is not unusual in hydrogenation with Raney-nickel[5-7]. It was identified as 6α-amino-5-cyano-5α-cholestane (XI) by direct comparison (m.m.p., co-TLC and IR) with an authentic sample obtained from VII.

Experimental Procedure

Melting points are uncorrected. IR spectra in KBr were recorded on a Pye-Unicam SP3-100 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in $CDCl_3$ on a Varian A60 instrument using TMS as internal standard (chemical shifts in δ, ppm). Hydrogenation was carried out in a Parr catalytic hydrogenation apparatus.

5-Cyano-6α-nitro-5α-cholestanes (V-VIII):
General method

A solution of the substrate (I-IV; 5 g) in ethanolic ether (100 ml; 3:2) was poured over naked KCN in excess and the reaction mixture kept at room temperature for 5-8 hr. After the completion of reaction (progress monitored by TLC), the solvent was evaporated under reduced pressure in a fuming chamber, and the residue mixed with a large excess of water, extracted with ether, ethereal layer washed with water and dried over anhyd. sodium sulphate. Removal of solvent followed by crystallization of the residue from pet. ether (60-80°)-ether gave the corresponding cyano compound (except in the case of nitroolefin II which gave a mixture of products V and VI which were separated by column chromatography over silica gel, and the hydroxy compound V, thus obtained, was acetylated with Ac_2O/Py to get VI). The characterization data of V-VIII are given in Table 1.

Hydrogenation of V with Raney-nickel: Formation of 6α-amino-5-cyano-3β-hydroxy-5α-cholestane (X)

A mixture of V (1 g), methanol (50 ml) and freshly prepared Raney-nickel in excess was hydrogenated at 30 psi for 2 hr when the reaction was found to be complete. [The reaction was also carried out at varying

Table 1—Characterization Data of 5-Cyano-6α-nitro-5α-cholestanes (V-VIII)

Compd	m.p. °C	Mol. formula	Found (%) (Calc.)			IR (cm^{-1})	PMR (δ, ppm)
			C	H	N		
V	140	$C_{28}H_{46}N_2O_3$	73.4 (73.8	10.1 10.0	6.1 6.1)	3420 (br, OH), 2250 (C≡N), 1560, 1370 (NO_2)	4.55 (*m*, 1H, $W_{1/2}$ = 17 Hz, C_6-βH), 3.97 (*m*, 1H, $W_{1/2}$ = 18 Hz, C_3-αH), 3.20 (*br s*, 1H, exchangeable with D_2O, C_3-*OH*), 1.07 (*s*, 3H, C_{10}-CH_3) and 0.67 (*s*, 3H, C_{13}-CH_3)
VI	213	$C_{30}H_{48}N_2O_4$	72.1 (72.0	9.6 9.6	5.6 5.6)	2245 (C≡N), 1740 (acetate CO), 1565, 1370 (NO_2), 1248, 1040 (C−O)	5.30 (*m*, 1H, $W_{1/2}$ = 19 Hz, C_3-αH), 4.73 (*m*, 1H, $W_{1/2}$ = 19 Hz, C_6-βH), 2.01 (*s*, 3H, C_3-$OCOCH_3$), 1.10 (*s*, 3H, C_{10}-CH_3) and 0.70 (*s*, 3H, C_{13}-CH_3)
VII	160 (lit.[1] 161)	-	-	-	-	2245 (C≡N), 1560, 1390 (NO_2)	4.50 (*m*, 1H, $W_{1/2}$ = 16 Hz, C_6-βH), 1.00 (*s*, 3H, C_{10}-CH_3) and 0.65 (*s*, 3H, C_{13}-CH_3)
VIII	143	$C_{28}H_{45}N_2O_2Cl$	76.0 (76.0	10.5 10.4	6.3 6.3)	2240 (C≡N), 1560, 1380 (NO_2), 780, (C−Cl)	4.50 (*m*, 1H, $W_{1/2}$ = 18 Hz, C_6-βH), 4.20 (*m*, 1H, $W_{1/2}$ = 18 Hz, C_3-αH), (both signals partially overlapping), 1.10 (*s*, 3H, C_{10}-CH_3) and 0.67 (*s*, 3H, C_{13}-CH_3)

pressures (20 to 50 psi) but the product was invariably the same]. Thereafter, Raney-nickel was filtered and the solvent removed to get an oily residue which was extracted with chloroform. The organic extract was washed repeatedly with water, dried, solvent removed and the residue crystallized from methanol to give X, m.p. 185°, yield 0.85 g; PMR: 4.0 (*m*, 1H, $W_{1/2}$ = 19 Hz, C_3-αH), 3.40 (*br m*, 1H, exchangeable with D_2O, C_3-βOH), 2.80 (*m*, 1H, $W_{1/2}$ = 24 Hz, C_6-βH), 2.10 [2H (mixed with methylene envelope), exchangeable with D_2O, NH_2 protons], 0.95 (*s*, 3H, C_{10}-CH_3), 0.65 (*s*, 3H, C_{13}-CH_3), 0.90 and 0.81 (other methyl protons) (Found: C, 78.5; H, 11.3; N, 6.5. $C_{28}H_{48}N_2O$ requires C, 78.5; H, 11.2; N, 6.5%).

Hydrogenation of VI (1 g) in a similar way also furnished X (m.p., m.m.p., co-TLC and IR), yield 0.70 g.

Hydrogenation of 5-*cyano*-6α-*nitro*-5α-*cholestane* (*VII*): *Formation of* 6α-*amino*-5-*cyano*-5α-*cholestane* (*XI*)

Compound VII (1 g) on treatment with hydrogen gas and Raney-nickel at 30 psi, followed by work-up of the reaction mixture as described above gave XI, m.p. 120°, yield 0.75 g; PMR: 2.75 (*m*, 1H, $W_{1/2}$ = 22 Hz, C_6-βH), 2.00 [2H, (merged with methylene envelope), exchangeable with D_2O, NH_2 protons] 0.95 (*s*, 3H, C_{10}-CH_3), 0.68 (*s*, 3H, C_{13}-CH_3), 0.93 and 0.83 (other methyl protons) (Found: C, 81.6; H, 11.6; N, 6.7. $C_{28}H_{48}N_2$ requires C, 81.6; H, 11.70; N, 6.7%).

Hydrogenation of VIII (1 g) in a similar manner also gave XI (m.p., m.m.p., co-TLC and IR), yield, 0.5 g.

5-*Cyano*-6α-*nitro*-5α-*cholestan*-3-*one* (*IX*)

Compound V (1 g) in acetone (10 ml) was treated with Jone's reagent (2 ml) at 0-5°. After 15 min, the reaction mixture was poured into water and extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (~5%) and water, dried (anhyd. Na_2SO_4), solvent removed and the crude product crystallized from ethanol to give IX, m.p. 155°, yield 0.7 g; IR: 2245 (C≡N), 1725 (C=O), 1565, 1375 (NO_2); PMR: 4.75 (*m*, 1H, $W_{1/2}$ = 20 Hz, C_6-βH), 1.2 (*s*, 3H, C_{10}-CH_3), 0.70 (*s*, 3H, C_{13}-CH_3), 0.92 and 0.98 (other methyl protons) (Found: C, 73.6; H, 9.6; N, 6.1. $C_{28}H_{44}N_2O_3$ requires C, 73.7; H, 9.7; N, 6.1%).

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Synthesis of 5α-Cyanocholestan-6-ones

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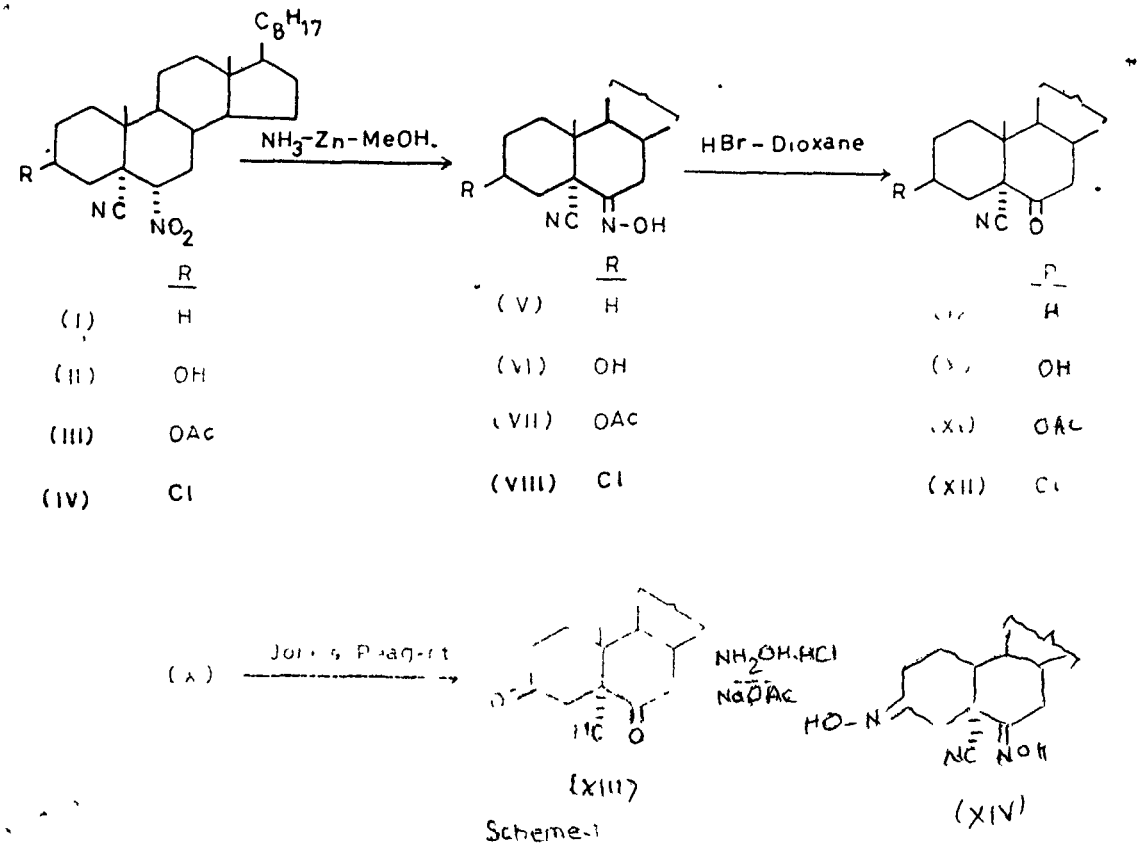
Synthesis of 5α-cyanocholestan-6-ones (IX-XII) from the respective oximes (V-VIII) obtained by the reaction of nitrocyanides (I-IV) with NH_3-Zn-MeOH, is described From X, 5α-cyanocholestane-3,6-dione (XIII) and subsequently dioxime (XIV) have also been obtained These cyanosteroids which are otherwise difficult to prepare form a series of new useful substrates

In the recent past a number of papers[1-4] describing the synthesis of β-cyanoketones through the Michael condensation of steroidal α,β-unsaturated ketones with KCN have been published But, the steroidal α-cyanoketones perhaps due to the lack of a clear-cut procedure for their synthesis could not be reported In the present synthesis of 5α-cyanocholestan-6-ones, our earlier procedure[5] for the preparation of oximes from steroidal nitroolefins has been successfully employed and its validity demonstrated in oximating 5α-cyano-6-nitrocholestanes (I-IV)[6] with the reagent NH_3-Zn-MeOH The oximes V-VIII thus obtained were hydrolysed to the respective 6-ones (IX-XII) in excellent yields by a selective solvent system consisting of hydrobromic acid and dioxane Oxidation of X with Jone's reagent furnished XIII, which on treatment with NH_2OH HCl/NaOAc produced the dioxime XIV (Scheme 1)

The products V-XIV were characterized on the basis of their elemental analyses and spectral data (IR and PMR) (Table 1) In particular, the oximes V-VIII showed in their IR spectra absorption bands at 3500-3400 (NOH) and 1650-1670 cm^{-1} (C=N) which are typical of oximes Their PMR spectra displaying a doublet around δ 3 40 for one of the C-7 protons and a one-proton singlet in the region 8 5-9 8 assignable for the oxime OH proton, fully supported the structures assigned to them

The notable feature in the IR spectra of the cyanooximes is the appearance of comparatively sharp bands (very sharp in the case of oxime VIII) shifted slightly to longer wavelengths (3500-3400 cm^{-1}) in



	R
(I)	H
(II)	OH
(III)	OAc
(IV)	Cl

	R
(V)	H
(VI)	OH
(VII)	OAc
(VIII)	Cl

	R
(IX)	H
(X)	OH
(XI)	OAc
(XII)	Cl

(XIII) (XIV)

Scheme-1

Table 1 - Characterization Data of the Products V-XIII

Compd	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	N	IR (cm^{-1})	PMR (δ, ppm)
V	70	178	$C_{28}H_{46}N_2O$	78.8 (78.9)	10.9 (10.8)	6.6 (6.6)	–	8.83 (*s*, 1H, N–OH*), 3.36 (*d*, J = 11 Hz, 1H, C_7-H), 0.90 (*s*, 3H, C_{10}-CH_3), 0.63 (*s*, 3H, C_{13}-CH_3), 0.86 and 0.83 (other methyl protons)
VI	75	215	$C_{28}H_{46}N_2O_2$	76.1 (76.0)	10.5 (10.4)	6.4 (6.3)		9.80 (*s*, 1H, N–OH*), 4.20 (*m*, $W_{\frac{1}{2}}$ = 20 Hz, 1H, C_3-αH), 3.85 (broad *s*, 1H, C_3-OH*), 3.35 (d-like, J = 10 Hz, 1H, C_7-H), 0.90 (*s*, 3H, C_{10}-CH_3), 0.67 (*s*, 3H, C_{13}-CH_3), 0.87 and 0.82 (other methyl protons)
VII	70	221	$C_{30}H_{48}N_2O_3$	74.5 (74.4)	10.0 (9.9)	5.9 (5.8)	–	8.50 (sharp *s*, 1H, N–OH*), 5.20 (*m*, $W_{\frac{1}{2}}$ = 20 Hz, 1H, C_3-αH), 3.35 (*d*, J = 11 Hz, 1H, C_7-H), 2.05 (*s*, 3H, (C_3-$OCOCH_3$), 0.94 (*s*, 3H, C_{10}-CH_3), 0.67 (*s*, 3H, C_{13}-CH_3), 0.87 and 0.82 (other methyl protons)
VIII	72	182	$C_{28}H_{45}N_2OCl$	72.9 (73.0)	9.9 (9.8)	6.0 (6.1)	–	8.53 (sharp *s*, 1H, N–OH*), 4.30 (*m*, $W_{\frac{1}{2}}$ = 22 Hz, 1H, C_3-αH), 3.40 (*d*, J = 10 Hz, 1H, C_7-H), 0.91 (*s*, 3H, C_{10}-CH_3), 0.67 (*s*, 3H, C_{13}-CH_3), 0.83 and 0.88 (other methyl protons)
IX	80	119	$C_{28}H_{44}NO$	81.7 (81.8)	11.0 (11.0)	3.4 (3.4)		2240 (C ≡ N), 1725 (C = O)
X	85	105	$C_{28}H_{45}NO_2$	78.8 (78.7)	10.5 (10.5)	3.2 (3.2)		3400 (broad, C_3-OH), 2230 (C ≡ N), 1725 (C = O)
XI	80	122	$C_{30}H_{47}NO_3$	76.8 (76.8)	10.1 (10.0)	3.1 (3.0)		2235 (C ≡ N), 1725 (C = O), 1730 ($OCOCH_3$) (merged together), 1230, 1050 (C – O)
XII	80	147	$C_{28}H_{44}NOCl$	75.5 (75.4)	9.9 (9.9)	3.2 (3.1)		2230 (C ≡ N), 1730 (C = O), 760 (C – Cl)
XIII	80	191	$C_{28}H_{43}NO_2$	79.1 (79.1)	10.2 (10.1)	3.3 (3.3)		2230 (C ≡ N), 1730 (3-CO), 1710 (6-CO)

*Exchangeable with D_2O.

contrast to the broad absorption bands for the corresponding OH stretching in 6-oximino-5α-cholestanes[5]. This phenomenon can be explained by considering the intramolecular hydrogen bonding[7,8] between the oxime OH and CN groups in these products. The hydrolysis of the cyanooximes to the ketones taking longer reaction period and higher temperature supports the above viewpoint.

A noteworthy point regarding the IR spectra of the cyanoketones is a 15-20 cm^{-1} increase in the frequency of C-6 carbonyl group in comparison to the normal frequency of this function in α-unsubstituted steroidal 6-ones. This is due to the presence of CN group α to the carbonyl group which shifts the νC = O band to a higher frequency as has been observed in the case of α-haloketones[9]. This effect is quite evident in the IR spectrum of the cyanodiketone XIII which exhibited a bifurcated band at 1710 and 1730 cm^{-1}. The latter band can be unambiguously assigned to the C-6 carbonyl function while the former appearing at the normal value corresponds to the C-3 carbonyl function.

Melting points are uncorrected. IR spectra were recorded in KBr on a P.U. SP3-100 infrared spectrophotometer (ν_{max} in cm^{-1}), and PMR spectra in $CDCl_3$ on a Varian A 60 instrument using TMS as internal standard (chemical shifts in δ, ppm).

5α-Cyano-6-oximinocholestanes (V-VIII)

Zinc dust (6 g) was added to a stirred solution of 5α-cyano-6-nitrocholestane (2 g) in ether-methanol mixture (100 ml; 1:1) containing ammonia solution (sp. gr. 0.91; 40 ml) at room temperature (25-35°) and the progress of the reaction monitored by TLC. The reaction was over within 15-30 min. Thereafter, the suspension was filtered, the filtrate reduced on a

steam-bath, the residue mixed with a large amount of water and extracted with ether. The ethereal layer was washed with water, dried (anhyd. Na_2SO_4), and the solvent evaporated to get a solid which on crystallization from methanol provided the corresponding oxime in 70-75% yield as shining crystal (another product formed in minute quantity was not characterized).

5α-Cyanocholestan-6-ones (IX-XII)

A solution of the appropriate oxime (1 g) in dioxane (25 ml) and HBr (10 ml; 40%) was refluxed on a heating mantel for varying periods (8-40 hr) and the progress of the reaction monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure and the residue extracted with ether. The ethereal layer was washed successively with water, sodium bicarbonate solution (~2%) and water, dried (anhyd. Na_2SO_4), filtered and the solvent evaporated on a steam bath. Crystallization of the residue from methanol-ether provided the corresponding cyanoketone in 80-85% yield.

5α-Cyanocholestane-3,6-dione (XIII)

To a stirred solution of X (1 g) in acetone (30 ml) and cooled to 0-5°, was added Jone's reagent (10 ml) dropwise during 20 min. The stirring was continued further for half an hour. The reaction mixture was then mixed with water, worked-up in the usual way with ether. Removal of the solvent gave a solid which was crystallized from methanol to give XIII, yield 0.8 g m.p. 191°.

5α-Cyano-3,6-dioximinocholestane (XIV)

A mixture of XIII (0.5 g) in methanol (30 ml), hydroxylamine hydrochloride (1.5 g) and sodium acetate (1 g) was warmed on a steam-bath for 20 min, poured into water and extracted with chloroform. The organic layer was washed with water, dried (anhyd. Na_2SO_4) and filtered. Evaporation of the solvent and crystallization of the residue from methanol gave the cyanodioxime XIV, yield 0.4 g, m.p. 245°, IR: 3620-3180 (broad, NOH), 2230 (C≡N), 1660 (C=N) (Found C, 73.8; H, 10.0; N, 9.2. $C_{28}H_{45}N_3O_2$ requires C, 73.9; H, 9.9; N, 9.2%).

The authors are grateful to Prof M S Ahmad, Chairman, Department of Chemistry for facilities and encouragement, and to the CSIR, New Delhi for financial assistance to two of them (MH and MH).

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Synthesis of 2,3-Dihydro-[2,3′-biindole]-1-carbonyl Chloride & Its Derivatives

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Synthesis of 2,3-Dihydro-[2,3'-biindole]-1-carbonyl Chloride & Its Derivatives

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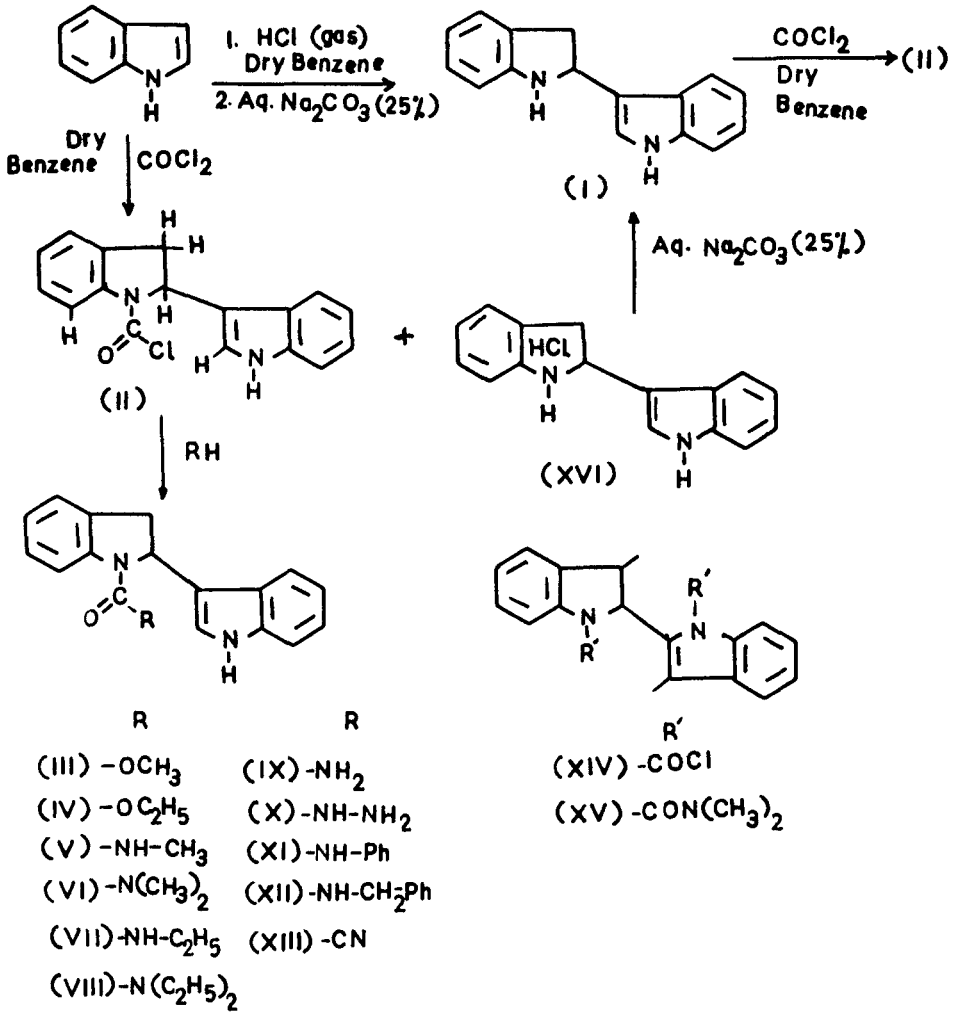
Indole or its dimer (I) on reaction with excess phosgene below 20°C gives 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (II). The latter compound reacts with a variety of reagents to give 1-substituted 2,3-dihydro-2,3'-biindoles (III-XIII). Structural assignments of all the products are based on elemental analyses and spectral (IR, PMR, mass) data.

Motivated by the medicinal importance of biindoles[1], we attempted the synthesis of a number of N-substituted indole dimers. Bergman *et al.*[2] reported that the reaction of 3-methylindole with $COCl_2$ yielded the biindole XIV which was isolated as the N,N-dimethylamide derivative (XV). In the present study, a similar treatment of indole and its dimer (I)[3] with phosgene, however, has produced 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (II), which is marked by the attachment of COCl group at the nitrogen of indoline moiety only—the indole moiety remains unaffected. This on treatment with suitable reagents furnished a variety of 1-substituted 2,3-dihydro-2,3'-biindoles (III-XIII; Table 1). Thus, the transformation of compound II into various products constitutes a facile method for obtaining biindoles with a suitable substituent at the nitrogen of indoline moiety.

The reaction of indole and indole dimer (I)[3] with an excess of phosgene afforded a compound, m.p. 132° (in the case of indole, dimer hydrochloride XVI was also obtained) which gave positive Beilstein test indicating the presence of halogen. The mass spectrum of this product exhibiting M^+ peaks at *m/z* 296 and 298 (3:1) also suggested the presence of chlorine in a dimeric compound as II. The fragment *m/z* 233 clearly showed the presence of carbonyl chloride moiety in the product. This was further supported by IR spectrum exhibiting absorption bands at 3320, 1690 and 820 cm^{-1} due to N–H, N–C(Cl)=O and C–Cl stretching frequencies respectively. The PMR spectrum[4] was in agreement with the assigned structure as 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (II). It displayed an uneven doublet of a doublet ($J_1 = 17$ Hz; $J_2 = 2.5$ Hz) at δ 3.15 integrating for one proton ascribable to C_3-H. Another one-proton doublet of a doublet ($J_1 = 17$ Hz; $J_2 = 9$ Hz) appearing at δ 3.85 could be assigned to the other C_3-proton. One more double doublet ($J_1 = 9$ Hz;

Table 1—Reaction Conditions and Characterization Data of Products IV-XIII

Product	m.p. (°C)	Yield (%)	Reaction conditions	Molecular formula	Found (%) (Calc.)		
					C	H	N
IV	136	82	EtOH (50 ml; 80%), $Ba(OH)_2$ (1 g), stirring for 2 hr	$C_{19}H_{18}N_2O_2$	74.58 (74.51)	6.00 5.88	9.10 (9.15)
V	183	75	$MeNH_2$ (5 ml) in THF (25 ml), 2 hr	$C_{18}H_{17}N_3O$	74.21 (74.23)	5.91 5.84	14.45 (14.43)
VI	190	85	Me_2NH (5 ml) in THF (25 ml), 2 hr	$C_{19}H_{19}N_3O$	74.81 (74.75)	6.19 6.23	13.72 (13.77)
VII	178	70	$EtNH_2$ (10 ml) in THF (25 ml), 2 hr	$C_{19}H_{19}N_3O$	74.71 (74.75)	6.29 6.23	13.80 (13.77)
VIII	169	60	Et_2NH (10 ml) in THF (25 ml), 1 hr	$C_{21}H_{23}N_3O$	75.63 (75.68)	6.99 6.91	12.54 (12.61)
IX	208	72	NH_3 (10 ml) in THF (30 ml), 2 hr	$C_{17}H_{15}N_3O$	73.59 (73.65)	5.50 5.42	15.21 (15.16)
X	185	80	NH_2-NH_2 (5 ml) in THF (25 ml), 2 hr	$C_{17}H_{16}N_4O$	69.95 (69.86)	5.41 5.48	19.09 (19.18)
XI	173	80	Ph-NH_2 (10 ml) in THF (25 ml), 3 hr	$C_{23}H_{19}N_3O$	78.16 (78.19)	5.45 5.38	11.98 (11.90)
XII	205	75	Ph-CH_2-NH_2 (5 ml) in THF (20 ml), 3 hr	$C_{24}H_{21}N_3O$	78.50 (78.47)	5.65 5.72	11.37 (11.44)
XIII	163	60	KCN (10 ml; 50%) in Dioxane (25 ml), 4 hr	$C_{18}H_{13}N_3O$	75.22 (75.26)	4.59 4.53	14.70 (14.63)



$J_2 = 2.5$ Hz) integrating for 1H and appearing at δ 5.95 was unmistakably[5] attributed to the proton on the carbon atom bearing amide and C=C groups (C_2-H of indoline moiety). A multiplet centred at δ 7.20 was assignable to aromatic (7H) and vinylic (1H) protons. A one-proton doublet like signal characteristic[6] of the aromatic proton in close proximity to C=O was observed at δ 8.00 and attributed to the C_7-H of indoline moiety. A broad signal (1H, exchangeable with D_2O) observed at δ 10.03 was due to NH proton of the indole moiety.

On the basis of the above spectral data, compound having m.p. 132°, was assigned the structure of 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (II). The confirmation of this structure came from the reaction of indole dimer (I) (obtained from the dimer hydrochloride XVI)[7] with phosgene furnishing exclusively a product identical (m.p., m.m.p. and co-TLC) with II. Compound II was smoothly converted into a number of its derivatives (III-XIII; Table 1).

Melting points were taken on a Kofler hot block and are uncorrected. Mass spectra were recorded on a JMS-300 mass spectrometer, IR spectra on a P-U-SP3-100 infrared spectrometer, and PMR spectra in $CDCl_3$ + DMSO – d_6 on a Varian A60 instrument using TMS as internal standard. TLC was performed on plates coated with silica gel G and spots were visualized with iodine vapours.

Reaction of indole with phosgene: Formation of 2,3-dihydro-[2,3'-biindole]-1-carbonyl chloride (II)

A solution of indole (3.0 g) in benzene (75 ml) was treated with phosgene gas (5.0 g) during 30 min with occasional shaking at a temperature below 20°C. The progress of the reaction was monitored by TLC. After the reaction was over (2 hr), the precipitated dimer hydrochloride (XVI)[7] was filtered off in a fuming chamber and the filtrate evaporated under reduced pressure by passing the vapours through 20% KOH solution or by exposing the filtrate to air in a fuming chamber (heating of the filtrate was avoided in order to get a single product). A crystalline material, thus separated, was filtered on a Buckner funnel and

recrystallized from ethyl acetate-benzene (2:3) (1.8 g), m.p. 132°; MS: *m/z* 296, 298 (M^+ 7.5; 2.5%), 261 ($M^+ - Cl$; 90.4%), 260 ($M^+ - HCl$; 100%, base peak), 233 ($M^+ - COCl$; 9.14%), 117 ($C_8H_7N^+$; 19.23%); IR(KBr): 3320 (NH), 3080, 3020 (C=C–H), 1690 (N–C(=O)–Cl), 1590, 1540 (C=C), 820 cm^{-1} (C–Cl).

1-Carbomethoxy-2,3-dihydro-2,3'-diindole (III)

Compound II (1.0 g) was treated at room temperature with methanol (50 ml; 80%) in the presence of $Ba(OH)_2$ (1.0 g) for 2 hr with occasional shaking. After the reaction was over, the solvent was reduced to 10 ml and the contents were poured into cold water and extracted with ether. The ethereal layer was washed twice with water, dried (anhyd. Na_2SO_4) and solvent removed to give an oily residue which was crystallized from methanol (0.80 g), m.p. 173°; MS: *m/z* 292 (M^+, 86.32%), 261 ($M^+ - OCH_3$; 8.35%), 233 ($M^+ - OCOCH_3$; 60.3%), 117 (100%; base peak), ($C_8H_7N^+$); IR(KBr): 3300 (–NH), 3080, 3020 (C=C–H), 1675 (N–C(=O)–OCH_3), 1590, 1540 (C=C), 1120, 1050 (C–O), 750 cm^{-1} (substituted benzene); PMR: δ3.15 (*dd*, $J_1 = 17$ Hz; $J_2 = 2.5$ Hz, 1H, C_3-H of indoline moiety), 3.75 (*dd*, $J_1 = 17$ Hz; $J_2 = 9$ Hz, 1H, C_3-H of indoline moiety), 3.67 (*s*, 3H, $COOCH_3$), 5.80 (*dd*, $J_1 = 9$ Hz; $J_2 = 2.5$ Hz, 1H, C_2-H indoline moiety), 7.28 (*mc*, 8H, 7 aromatic + 1 vinylic protons), 7.75 (*d*, 1H, C_7-H of indoline moiety), 10.07 (*br s*, 1H, exchangeable with D_2O, NH of indole moiety).

Compound II (1 g) was also treated at room temperature with different reagents for varying periods and the reaction mixture in each case worked-up as above. The reaction conditions and the characterization data of compounds IV-XIII, thus prepared, are given in Table 1.

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A Novel Thermal Rearrangement of 2,3-Dihydro-2-(indol-3-yl)indole-1-carbonyl Chloride and its Amino Derivatives[1] †

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A Novel Thermal Rearrangement of 2,3-Dihydro-2-(indol-3-yl)indole-1-carbonyl Chloride and its Amino Derivatives[1] †

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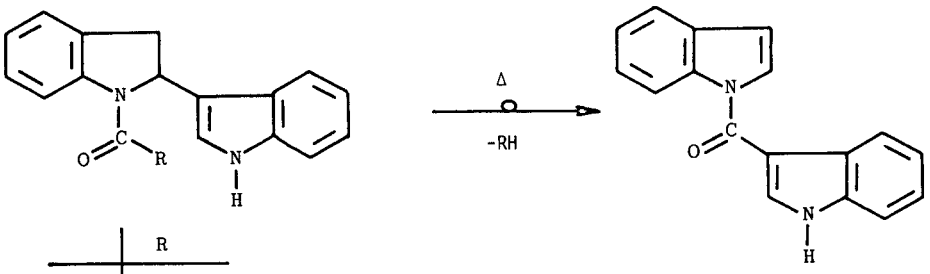
The formation of 1,3′-carbonylbi-indole (**7**) from 2,3-dihydro-2-(indol-3-yl)indole-1-carbonyl chloride (**1**) and its amino derivatives (**2**)–(**6**) is reported; the mechanism of the reaction, which involves a novel type of rearrangement, is also discussed.

The partial change of compound (**1**), even at room temperature motivated a study of the driving force that initiates this transformation. The substrate (**1**) and its derivatives (**2**)–(**6**), on direct heating or in the presence of a solvent, were smoothly converted in high yield into a product identified as 1,3′-carbonylbi-indole (**7**) by comparison (m.p. and spectral properties) with an authentic specimen.[2]

An interesting feature in the formation of the product (**7**) is the migration of the indole system to the carbonyl group, followed by deprotonation. A probable mechanism for the transformation (**1**) → (**7**) is outlined in the Scheme.

The attack of the electrophilic centre by the relatively electron rich C-3′ of the indole ring leads to a carbonium ion at C-2′ which is further resonance stabilized by the lone pair of the adjacent nitrogen. Attack at C-2′ is not so likely as the resultant carbonium ion at C-3′ would not be as favourable. The greater stability of the resonance-stabilized carbonyl group in (**7**), compared to that in the substrates (**1**)–(**6**), provides the driving force necessary



	R
(**1**)	Cl
(**2**)	NHMe
(**3**)	NHEt
(**4**)	NMe_2
(**5**)	NEt_2
(**6**)	$NHCH_2Ph$

(**7**)

The product (**7**), m.p. 226 °C (lit.,[2] 227 °C) analysed for $C_{17}H_{12}N_2O$ and showed a molecular ion peak at *m/e* 260 and a base peak at *m/e* 117. Its i.r. spectrum showed absorption bands at 3320 and 1650 cm^{-1}, compatible with —NH and —N—C(=O)—C=C— stretching frequencies, respectively. The ^1H n.m.r. spectrum showed a multiplet centred at δ 7.30 for 10 protons (7 aromatic + 3 vinylic) and a doublet-like signal[1] for 1 proton (7-H) in close proximity to a C=O. A broad signal for one proton at δ 10.7 (exchangeable with D_2O) assignable to an NH proton indicated the presence of only one NH proton thus showing that the carbonyl group is linked to one of the nitrogen atoms.

for the cleavage of the C—C linkage.

Other products formed in minute quantities were not isolated. However, some of the products formed during the reaction of indole with phosgene[2] can be explained by assuming the substrate (**1**) to be the intermediate.

Experimental

General Method for the Preparation of 1,3′-*Carbonylbi-indole* (**7**). – The starting bi-indole (**1**)–(**6**)[1] (1 g) was heated on a mantel until it melted [(**1**), 132 °C; (**2**), 183 °C; (**3**), 178 °C; (**4**), 190 °C; (**5**), 169 °C; (**6**), 205 °C]. It was then cooled, and heated again to its m.p. This process was repeated for 30 min, at which time the reaction was complete (t.l.c.). The solid was dissolved in ethyl acetate and the solution was washed successively with water, sodium hydrogen carbonate solution (*ca.* 2% w/v), and more water and dried (Na_2SO_4). Removal of the solvent gave a solid which was chromatographed on a silica gel column to afford the product (**7**) (0.6–0.7 g, 60–80%), m.p. 226 °C (from MeOH) (lit.,[2] 227 °C); ν_{max} (Nujol) 3320 and 1650 cm^{-1}; δ_H ($CDCl_3$–[$^2H_6$]Me_2SO) 7.30 (10 H, m, 7 aromatic + 3 vinylic), 7.6 (1H, d, 7-H) and 10.7 (1 H, br s, NH, exchangeable); *m/e* 260 (M^+, 19.7%) and 117 (100%) (Found: C, 78.4; H, 4.7; N, 10.6. Calc. for $C_{17}H_{12}N_2O$: C, 78.46; H, 4.62; N, 10.77%).

* To receive any correspondence.

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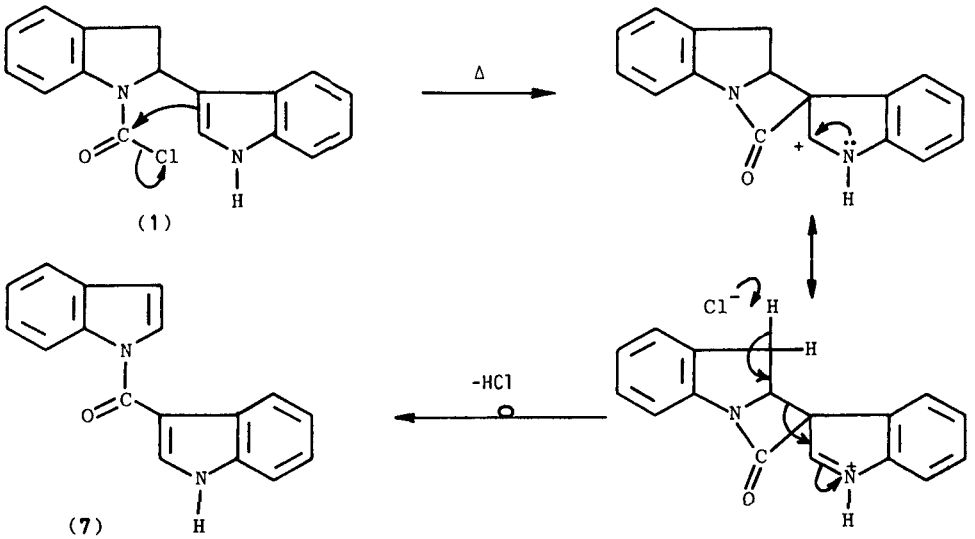

Scheme

The product (**7**) could also be prepared from (**1**), in particular by the following procedures

(*a*) A solution of compound (**1**) (1 g) in benzene (50 ml) was refluxed on a steam-bath for 2 h, by which time the reaction was complete The benzene was removed and the residue dissolved in ethyl acetate This solution was then washed repeatedly with water and dried (Na_2SO_4) Removal of the solvent provided a solid which was purified on a silica gel column to yield (**7**) (0 5 g, 57%)

(*b*) Compound (**1**) (1 g), on treatment with 10% aqueous KOH (50 ml) at reflux temperature for 1 h followed by usual work-up, furnished the product (**7**) in better yield (0 7 g, 79 5%).

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